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The American Journal of Medicine

Vol. XVII DECEMBER, 1954 No. 6

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"A high level of suspicion regarding the biliary tract as a cause of dyspepsia will be rewarding."

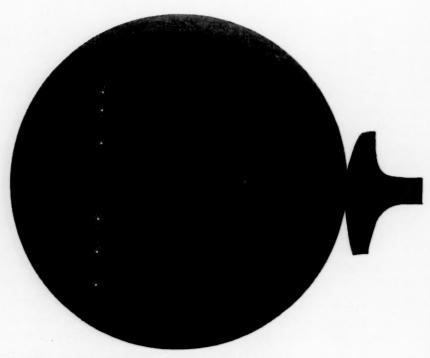
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 O'Brien, G. F., and Schweitzer, I. L.:
 M. Clin. North America 37:155 (Jan.) 1953.

2. Rising, J. D.: Missouri Med. 51:52, 1954.

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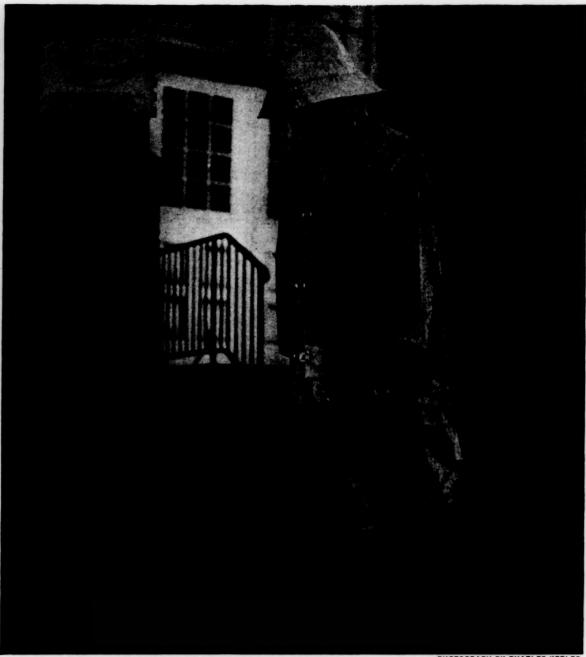
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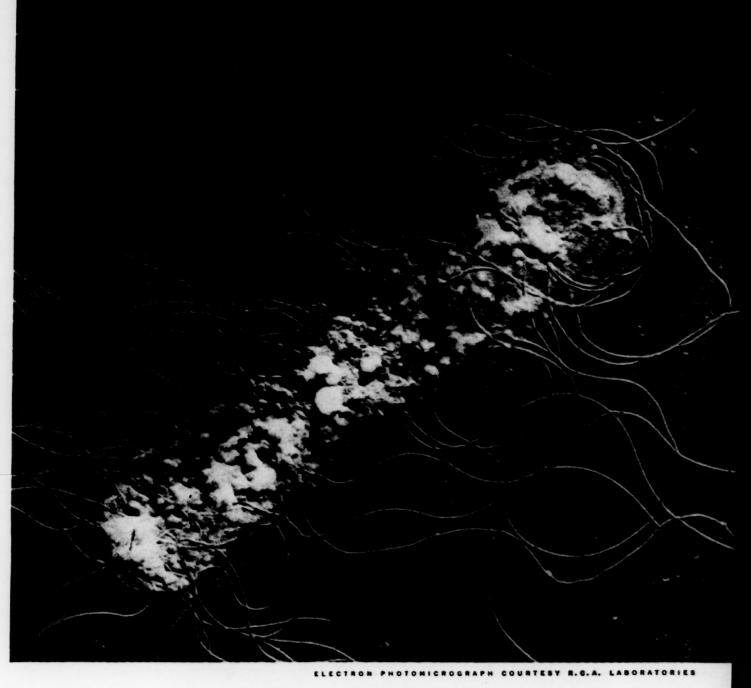


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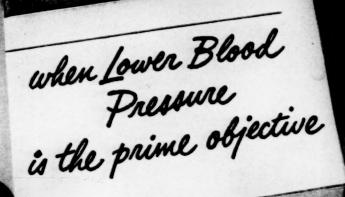
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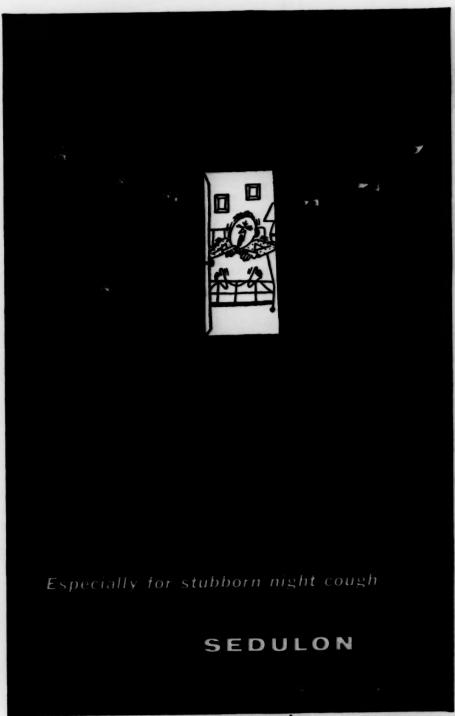
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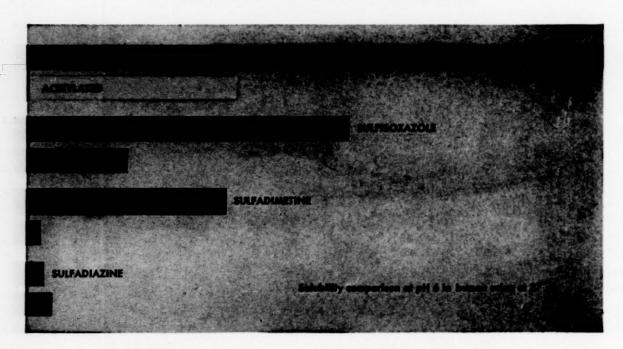
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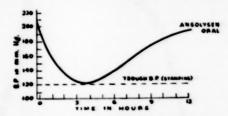
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- 1. Freis, E. D.: Personal communication
- Sturgis, C. C.: Television Symposium; "The Management of Hypertension," American College of Physicians, Sept. 23, 1954
- 3. Smirk, F. H.: Lancet 1:457 (March 7) 1953
- Freis, E. D.: M. Ann. District of Columbia 23:363 (July) 1954
- 5. Smirk, F. H., and others: Lancet 2:159 (July 24) 1954

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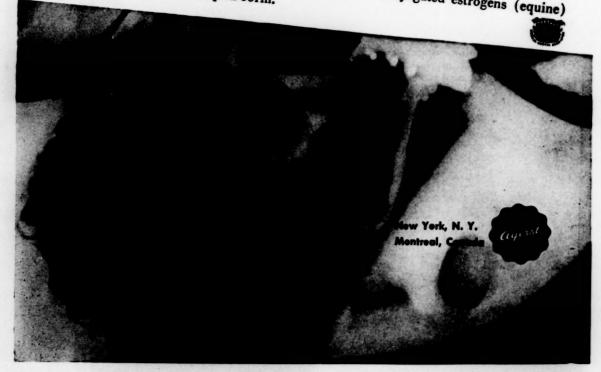
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Klohs, M. W.; Draper, M. D., and Keller, F.: J. Am. Chem. Soc. 76:2843 (May 20) 1954.

Cronheim, G.; Brown, W.; Cawthorne, J.; Toekes, M. I., and Ungari, J.: Proc. Soc. Exper. Biol. & Med. 86:110 (May) 1954.

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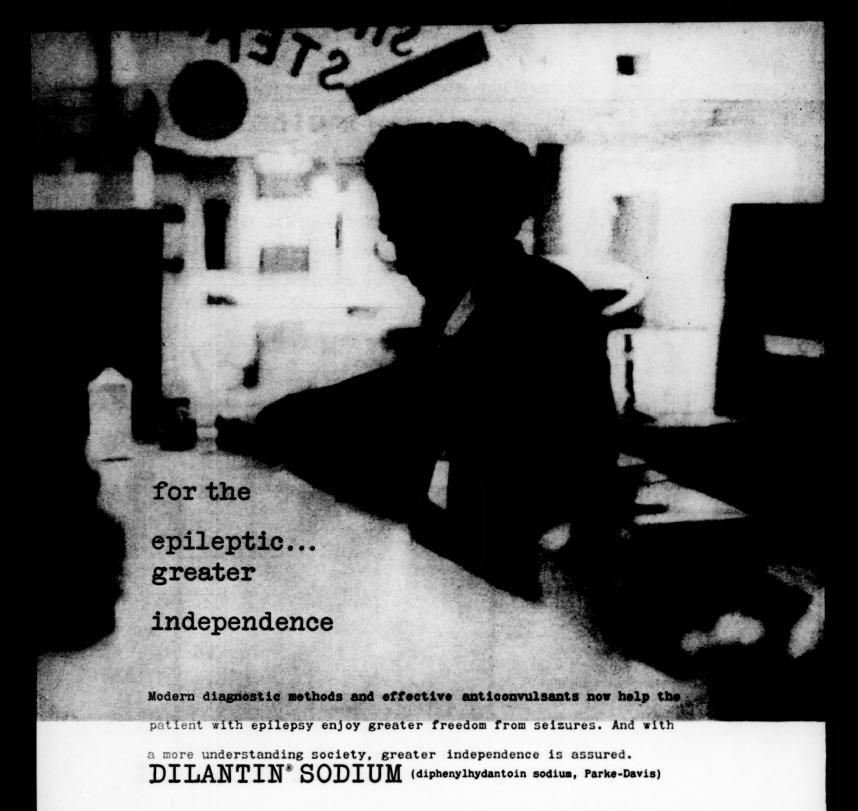
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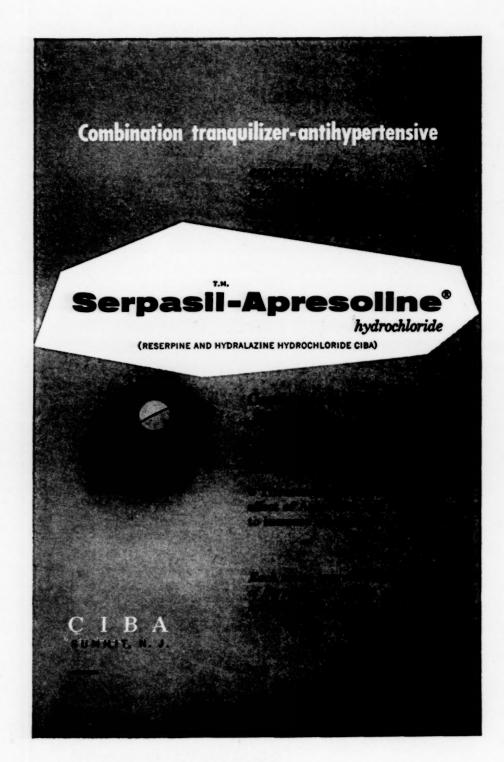
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The American Journal of Medicine

Vol. XVII

DECEMBER, 1954

No. 6

Foreword

THE increasing vigor of the attack on rheumatic fever during the past twenty-five years has resulted in significant progress toward solution of the manifold problems concerned with the disease. New developments have emerged from a variety of medical disciplines, ranging from investigative work on etiology to the introduction of methods for control and treatment of the acute disease and of surgical technics for correction of permanent valvular deformities. Although progress has perhaps not been so dramatic as in the case of certain other diseases, and it is clear that the present control measures do not represent final answers, the advances have nevertheless greatly improved the outlook for the rheumatic patient. This symposium represents an effort to summarize the current status of these developments in rheumatic fever and rheumatic heart disease.

A large gap remains in our knowledge of the mechanisms involved in the pathogenesis of rheumatic fever. However, even in this unsolved problem of the fundamental nature of the disease, it must be conceded that a major contribution has been made in establishing the fact that infections with hemolytic streptococci initiate the rheumatic state. The view that streptococcal infection is an integral part of the disease gradually gained wider acceptance during the years just preceding the introduction of the sulfonamide drugs and was responsible for the initial attempts to prevent recurrences of rheumatic fever by continuous prophylaxis with sulfanilamide. In turn, the success of these and subsequent prophylactic experiments served to provide further support for the role of the streptococcus. The concept is now thoroughly substantiated and it will be noted that much of what is said in this symposium concerning such aspects of the disease as prevention and diagnostic tests is directly related to the streptococcal origin of the disease.

The major recent development in the treatment of acute rheumatic fever is the introduction of the use of adrenocorticotrophic hormone and cortisone. It would appear at present that these substances have fallen somewhat short of their promise of revolutionizing therapy of the disease. However, the final evaluation of hormonal therapy cannot yet be made; and because of the well recognized extreme variability in the course and outcome of rheumatic fever, a long and painstaking analysis of these new agents will be required to determine whether they affect the occurrence of permanent cardiac malformations.

The current era of cardiac and vascular surgery has offered the first opportunity to deal effectively with the chronic invalidism resulting from mechanical deformation of cardiac valves in rheumatic patients. In addition, because the surgical technics now available are limited to the correction of certain specific anomalies, principally mitral stenosis, the accurate anatomic diagnosis of rheumatic heart disease has been converted from a largely academic problem to an intensely practical one, and a considerable impetus has been given to the development of new diagnostic procedures. The problems of diagnosis and selection of patients for surgery are discussed from several points of view in the symposium, followed by an evaluation of the surgical approach and consideration of a unique and puzzling complication of surgery in rheumatic subjects.

Among the contributions to our knowledge of the disease that are regrettably not represented in the symposium are the long-term studies on the natural history of rheumatic fever. These studies, notably the admirable twenty-year report of Bland and Jones, involve the continued observation by competent clinicians of large numbers of rheumatic patients over a long period

¹ Bland, E. F. and Jones, T. D. Circulation, 4: 836 1951.

of time, and they have increased the precision of our concepts concerning the course of events and prognosis in rheumatic fever. Obviously, there must be other omissions, since all facets of a disease as complex as rheumatic fever cannot be given adequate consideration in a short series of papers. However, it is hoped that collectively the papers will provide a clear picture of most aspects of major importance.

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Symposium on Rheumatic Fever and Rheumatic Heart Disease

The Role of the Streptococcus in the Pathogenesis of Rheumatic Fever*

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LTHOUGH the etiology of rheumatic fever is still considered to be obscure, there has been a steady accumulation of data linking the disease to infection with group A streptococci. Numerous surveys have demonstrated the occurrence of epidemics of rheumatic fever following outbreaks of scarlet fever and other streptococcal infections. 1-5 Serologic studies have shown that elevated titers of streptococcal antibodies occur in the serum of patients with rheumatic fever indicating recent contact with the streptococcus. 6-12 Further evidence relating the two diseases was obtained when it was shown that the incidence of rheumatic fever was greatly diminished by the prevention or treatment of streptococcal infections with antibacterial agents. 13-18

Despite the above evidence indicating that the group A streptococcus is responsible for rheumatic fever, a disturbing fact is that these organisms have been isolated from only 50 to 60 per cent of patients during the acute phases of rheumatic fever. ^{19,20} It has been assumed that if rheumatic fever is directly related to a streptococcal infection, nearly all of the patients should harbor streptococci during the acute disease. The success in isolating the streptococcus, however, is a function of the bacteriologic technics employed and the frequency with which cultures are obtained.

The ease with which group A streptococci

may be isolated from the oropharynges of rheumatic patients is no different than the ease with which these organisms may be recovered from patients convalescing from acute streptococcal tonsillitis. In Figure 1 are presented results of routine cultures of the oropharynges of 355

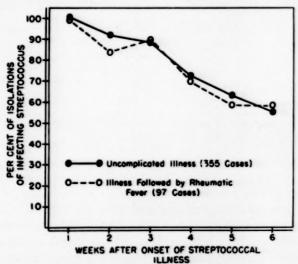


Fig. 1. Isolations of group A streptococci following an untreated streptococcal infection.

patients with uncomplicated acute streptococcal infections and ninety-seven patients whose acute illness was followed by rheumatic attacks. None of these patients received specific antibacterial therapy during the period of observation. At any one period following the streptococcal infection,

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the infecting type of streptococcus was isolated from an equal percentage of patients who developed rheumatic fever and of those who developed no complication. The number of patients shown to harbor streptococci at the weekly surveys decreased gradually so that by the sixth

TABLE 1
DISTRIBUTION OF PATIENTS ACCORDING TO TYPE
OF THERAPY*

Treatment Group	No. of Patients	Therapy		
First half of study: Control Penicillin9 day	288 301	No specific therapy 900,000 units of depot penicillin admin- istered on the ninth, eleventh and thir- teenth days after the		
Second half of study: Sulfadiazine	291	onset of illness Two gm. administered at time of admission to study		
Penicillin—9 day	297	followed by 1.0 gm. every six hours for five days 900,000 units of depot penicillin admin- istered on the ninth, eleventh and thir- teenth days after the		

^{*} Selection of patients for the various forms of therapy was determined by the Air Force serial number.

week only half the routine cultures from both groups of patients showed the infecting type of group A streptococcus. Studies to be reported elsewhere²¹ have demonstrated that group A streptococci can be isolated from all patients six weeks after a streptococcal illness if special bacteriologic procedures are employed. It appears likely, therefore, that most rheumatic subjects harbor the organism at the onset of the acute attack, but because of technical difficulties the streptococci have not been isolated and identified.

With the advent of penicillin therapy of streptococcal infections further investigation into the factors responsible for rheumatic fever became possible. Such treatment markedly reduces the attack rate of rheumatic fever, decreases the antibody response and eradicates the streptococcus from most patients. Since rheumatic patients frequently exhibit an exaggerated response to streptococcal antigens as compared

with patients who do not develop this complication, 7.9,10,12 one obvious conclusion is that the inhibition of antibody production is in some manner responsible for the prevention of rheumatic fever. On the other hand, despite a low antibody response following an infection treated with various antibiotics, rheumatic fever still developed in a few patients. An analysis of these patients revealed that most of them continued to harbor the infecting type of streptococcus.²² Thus it appeared that the persistence of the streptococcus after infection might be significant in the pathogenesis of rheumatic fever.

The present study was designed to determine the relative importance of the group A streptococcus and of excessive antibody production in the pathogenesis of rheumatic fever. For this purpose, patients with streptococcal infections were treated by one of three methods. In one group of patients, the streptococcus was eradicated by treatment with penicillin, but therapy was delayed until late in the course of the illness at a time when near maximal antigenic stimulation had already occurred. In a second group of patients, the production of antibody was inhibited without eradication of the streptococcus. This was accomplished by the administration of sulfadiazine during the acute illness. A third group of patients who received placebo injections served as controls and thus remained carriers and sustained maximum antibody production.

METHODS AND DESCRIPTION OF STUDY

The methods of selection of patients and of the routine clinical and laboratory studies were similar to those previously reported.¹⁷ The patients consisted of young adult airmen admitted to the hospital with exudative tonsillitis or pharyngitis. Historical information, physical examination and laboratory studies were accomplished in a standard manner at the time of admission to the hospital and nine, thirteen, twenty-one and thirty-five days after the onset of symptoms. The criteria for the diagnosis of rheumatic fever were those of Jones²³ with slight modifications.¹⁷

Chronologically, the study was divided into two parts. (Table I.) The first portion, conducted from January, 1953 to April, 1953, consisted of 301 men who received penicillin and 288 men who were given placebos and served as controls. Procaine penicillin in oil containing 2 per cent aluminum monostearate was administered intramuscularly in doses of 900,000 units on the

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ninth, eleventh and thirteenth days after the onset of illness. The second portion of the study, conducted from April, 1953 to January, 1954, consisted of 297 patients who received penicillin as described previously and 291 patients who were given sulfadiazine. Two gm. of sulfadiazine

patients who had streptococcal pharyngitis, the analysis was limited to those patients who had group A streptococci isolated from the initial culture of the throat. Of the 103 patients from whom group A streptococci were not isolated, 70 per cent were observed for twenty-one days.

TABLE II
COMPARABILITY OF TREATMENT GROUPS*

	Firs	st Half	Second Half		
	Control (220)	Penicillin 9 day (219)	Sulfadiazine (230)	Penicillin 9 day (201)	
	Per cent				
Family history of rheumatic fever	6.8	4.6	0.9	0.5	
Confluent exudate	15.9	21.5	18.6	11.4	
Leukocyte count of 12,000/cu. mm. or more	72.0	70.0	67.7	68.0	
Group A streptococci:		70.0	0,.,	00.0	
Type 3	23.5	18.6	17.6	18.8	
14		11.8	27.0	21.8	
19	27.7	26.8	14.1	15.8	
30	26.9	27.9	26.2	25.2	
Other types	13.9	11.8	15.1	18.4	
Antistreptolysin titer 125 units or less		73.1	74.5	73.8	
Onset of illness to admission to study:					
Less than 30 hr	56.5	57.6	51.8	49.7	
30–59 hr	37.3	29.6	35.1	41.7	
Greater than 59 hr	6.2	13.8	13.2	8.6	
Present for convalescent examination:					
21 days		98.6	87.4	95.0	
35 days	88.6	90.4	87.0	95.0	

^{*} Includes all patients maintained on the study from whom group A streptococci were isolated.

were administered at the time of admission to the hospital, following which each patient received 1 gm. every six hours for five days (21 gm. total).

Patients were excluded from the investigation if they exhibited evidence of a suppurative complication at the time of admission to the hospital, gave a personal history of rheumatic fever or had had a previous reaction to penicillin. During the second part of the study patients were also excluded if they had experienced a reaction to sulfadiazine or, in most instances, if there was a history of rheumatic fever in other members of the family.

COMPARABILITY OF STUDY GROUPS

During the period of this investigation there was a high incidence of non-streptococcal exudative pharyngitis. In order to include only DECEMBER, 1954

In one patient in this group rheumatic fever developed twenty-seven days from the onset of the acute illness for which he had received no specific therapy.

Suppurative complications characteristically occur during the early phases of the strepto-coccal infection. In the first portion of the study the incidence of suppurative complications was high since neither group of patients received specific therapy until the ninth day of illness when penicillin was administered to half of the patients. During the second portion of the study the patients who did not receive penicillin until the ninth day also developed suppurative complications. The patients who received sulfadiazine experienced a lower incidence of such complications.²⁴ In all instances penicillin was administered to those patients in whom suppurative complications developed and they were then

excluded from the analysis. Many of these patients were followed during convalescence and none was observed to develop rheumatic fever. Thus the final analysis was based on the following groups: in the first half of the study 220 patients were in the control group and 219 received

TABLE III

PERSISTENCE OF THE INFECTING TYPE OF STREPTOCOCCUS
IN THOSE PATIENTS INITIALLY POSITIVE FOR TYPABLE

GROUP A STREPTOCOCCI

Treatment	No. of Pa-	Per cent	of Infecti ococcus*	ng Type	
	tients	9 days	13 days	21 days	35 days
First half					
Control	211	95	96	85	64
Penicillin-9 day	209	96	2	11	11
Second half					
Sulfadiazine	223	71	88	81	59
Penicillin-9 day	193	92	1	2	2

^{*} Patients were excluded at a given convalescent examination if a new serologic type of streptococcus was isolated.

penicillin; in the second portion 230 received sulfadiazine and 201 were given penicillin. Pertinent information obtained at the time of admission is listed in Table II. The number of patients having a family history of rheumatic fever was lower during the second half of the study due to the exclusion of most of such persons at the time of the original examination. The serologic types of streptococci isolated on admission varied in the two parts of the study in that type 14 became more prevalent and type 19 less prevalent during the second half.

RESULTS

The effects of the different forms of therapy on the infecting serologic type of streptococcus are summarized in Table III. The carrier rates in the untreated patients and in the penicillintreated patients were equal nine days after the onset of illness. At this time the infecting organism was isolated from a smaller number of those treated with sulfadiazine. Since sulfonamides have been shown to suppress the growth of streptococci,25 the low carrier rate in this group at nine days was probably a reflection of such bacterial inhibition. Although the carrier rates in the control and sulfadiazine-treated groups remained high throughout convalescence, the frequency of isolation of the organism by a single direct culture of the throat decreased as the period of time from the onset of illness lengthened. This apparent decrease in the carrier rates in the two groups was probably due to the technics employed for, as mentioned previously, if more adequate procedures had been used, all the patients probably would have been shown to harbor the infecting organism.

TABLE IV

EFFECT OF THERAPY ON ANTISTREPTOLYSIN RESPONSE IN
THOSE PATIENTS FROM WHOM TYPABLE GROUP A

STREPTOCOCCI WERE ISOLATED ON ADMISSION

	No. of Pa- tients	Average Antistreptolysin Titer No.						
Treatment		Admis- sion	9 days	21 days	35 days			
First half		units	units	units	units			
Control	211	118	174	339	339			
Penicillin—9 day Second half	209	113	168	293	291			
Sulfadiazine	223	112	148	245	270			
Penicillin-9 day	193	109	145	260	267			

In the patients who received penicillin therapy on the ninth day there was a marked fall in carrier rates on the thirteenth day and the rates remained low at subsequent examinations. No reason was found for the difference in the carrier rates in the penicillin-treated patients at twentyone and thirty-five days between the first and second part of the study.

The antistreptolysin responses to infection are recorded in Table IV. During the first part of the study the untreated patients showed an average increase of 221 units at twenty-one days as compared to 180 units in the penicillin-treated patients. Thus only an 18 per cent decrease in antibody response resulted from delaying penicillin therapy nine days after the onset of illness. Some of the difference in antibody production in the two groups was due to the acquisition of new infections during the interval between collection of the serum specimens. If the twenty-one control and six penicillin-treated patients who acquired a new type of streptococcus are excluded, the average increase in antibody was 202 and 181 units in the control and penicillin groups, respectively. This difference is not statistically significant.

During the second half of the study* those patients who were treated with penicillin devel-

^{*} None of the group of penicillin-treated patients acquired a new type of streptococcus. Six of the patients receiving sulfadiazine acquired a new serologic type of streptococcus, but excluding these individuals did not alter the average antibody titers.

oped slightly less antistreptolysin than the first group of penicillin-treated patients. In the patients who received sulfadiazine the average antistreptolysin response at twenty-one days was considerably less than that observed in the control group. At thirty-five days, however, the antibody titer in the sulfadiazine group increased over the titer recorded at twenty-one days, whereas in the other three study groups no such increase was observed. This increase in antibody titer late in convalescence was probably due to rapid proliferation of the organism after sulfadiazine was discontinued. Thus antigenic stimulation continued later in the course of the disease in those treated with sulfadiazine than in the other patients.

The occurrence of rheumatic fever in the various treatment groups is summarized in Table v. For purposes of comparison the cases are tabulated according to the interval from the onset of the streptococcal illness to the onset of rheumatic fever. The first division of nine days was the period of time before the penicillin groups received therapy. The next large division includes the tenth through the forty-fifth days. Previous studies have shown that when the latent period is less than thirty-five days, the observed streptococcal illness is apparently responsible for the rheumatic episode.17 Those cases which develop between the thirty-fifth and forty-fifth days are frequently due to the observed illness although a few patients may have acquired an intervening streptococcal infection. In the last division, where the interval was greater than forty-five days, experience has shown that an intervening infection usually is responsible for the attack of rheumatic fever.

The number of patients who developed symptoms of rheumatic fever during the first nine days was approximately equal in all four study groups. Since three of the groups of patients received no therapy during this period, the similar attack rates of rheumatic fever indicate that comparable groups were selected. Although sulfadiazine therapy administered during the first five days of hospitalization favorably altered the course of the acute illness,24 it failed to prevent rheumatic fever during this early period. Indeed, the attack rate of rheumatic fever was similar to that observed in the other three groups, suggesting that these patients did not differ in this regard from the other patients. From nine of the ten patients who developed symptoms of rheumatic fever during the first nine days the infecting type of streptococcus was again isolated at the time of onset of the complication.

Following the administration of penicillin on the ninth day of illness there was a striking decrease in acute rheumatic episodes. In contrast,

TABLE V
DISTRIBUTION OF CASES OF RHEUMATIC FEVER ACCORDING
TO THE INTERVAL FROM ONSET OF PHARYNGITIS TO
ONSET OF RHEUMATIC FEVER

	Number developing rheumatic fever						
Interval in Days	Control (220)	Penicillin 9-day (219) Sulfadiaz (230)		Penicillin 9-day (201)			
0-4 5-9	1 2	1 2	1 1	2 0			
10-14	3	0	4	0			
15-19	1	1	3	1			
20-24	1	0	1	0			
25-29	1	0	1	1			
30-35	0	0	3	0			
36-45	2	0	0	0			
>45	1	3	0	1			

the patients who received sulfadiazine experienced no protection against rheumatic attacks. Thus there was a total of twenty rheumatic episodes observed from the tenth to the forty-sixth day among the 450 sulfadiazine and placebo-treated patients. In contrast, 420 patients received penicillin after recovery from the acute streptococcal illness, and only three developed acute rheumatic fever during the same period.

Of the twenty patients in the two groups who received sulfadiazine or placebos, the infecting type of streptococcus was isolated from each man during the rheumatic episode. Group A streptococci were not isolated during the rheumatic attack from the three patients who received penicillin. The symptoms of the complication began fifteen, seventeen and twentynine days after the onset of the streptococcal illness in the latter patients and in each instance classic features of rheumatic fever were exhibited.

There were five rheumatic patients who devel-

oped symptoms later than forty-five days after the observed streptococcal infection, but none of these rheumatic attacks could be directly related to the observed illnesses. The patient in the control group had acquired a different serologic type of streptococcus during the interim. Of the four patients in the penicillin groups two had acquired different serologic types and two had experienced a sore throat during the intervening period.

In summary, the treatment of streptococcal infections with penicillin nine days after the onset of illness eliminated the infecting organism from the throat, failed to inhibit antibody formation appreciably, and significantly reduced the attack rate of rheumatic fever. In contrast, the administration of sulfadiazine during the acute streptococcal illness suppressed antibody formation somewhat more effectively than penicillin at twenty-one days, but did not eradicate the organism nor prevent rheumatic fever. The patients who received no specific therapy sustained maximum antibody formation, remained carriers and experienced the usual attack rate of rheumatic fever.

COMMENTS

These data indicate that penicillin therapy administered even after the acute symptoms of streptococcal infections have subsided will reduce the attack rate of rheumatic fever. Because of this observation, it is probably also advisable to administer penicillin to all patients observed in the early phases of acute rheumatic fever, under the assumption that eradication of the streptococcus may influence the rheumatic process. Certainly, further information as to the possible effects of such therapy is urgently needed.

The data also support the concept²² that even though a drug favorably influences the acute symptoms, it should not be used in the therapy of streptococcal infections unless adequate bacteriologic studies have established that such treatment results in elimination of the streptococcus from the respiratory tract. The prevention of rheumatic fever is the most important aspect of the therapy of these respiratory infections, and the evidence presently available indicates that rheumatic fever is not prevented unless the organism is eradicated.²² For this reason, it should be emphasized that sulfadiazine or other sulfonamides should never be

employed in the *treatment* of streptococcal infections. In the present study, sulfadiazine therapy did not result in elimination of the infecting organism and the incidence of rheumatic fever was even higher than in patients receiving placebo therapy.

In addition to these practical considerations, the data have certain theoretic implications with respect to the pathogenesis of rheumatic fever. In previous studies 17,18,22 it has been apparent that the prevention of rheumatic fever by treatment of streptococcal infections with penicillin could be correlated with eradication of the infecting organism and with suppression of antibody formation. It has not been possible, however, to dissociate these latter two effects or to determine which, if either, is of primary importance. In the present study, by withholding penicillin treatment until the convalescent phase of the streptococcal disease was well advanced, it has been possible to prevent rheumatic fever without suppressing significantly the antistreptolysin response. If the antistreptolysin response can be regarded as indicative of the response to other streptococcal antigens, it may be concluded that the prevention of rheumatic fever by penicillin treatment of streptococcal diseases is not related, in any direct or essential fashion, to the suppression of the immune response ordinarily seen. These data do not, of course, indicate that the immune response is not involved in the pathogenesis of rheumatic fever, but suggest that it is not of primary importance.

On the other hand, these results strongly indicate that the living streptococcus plays a more direct role in the production of rheumatic fever than has generally been considered. Although several investigators have isolated group A streptococci in a high percentage of cases²⁶⁻²⁸ from affected cardiac valves at autopsy, others have not found these organisms with any degree of regularity29 or have obtained negative results despite laborious attempts to culture the organisms from the heart, subcutaneous nodules, joints and blood. 30 If it be postulated that living streptococci are present in the affected tissues in rheumatic subjects, it is difficult to explain the non-suppurative character of the rheumatic lesions. However, eradication of streptococci by penicillin therapy in the present study was followed by a prompt fall in the number of new cases of rheumatic fever, and the most obvious interpretation of this finding is that the living

streptococci themselves must be present, in the oropharynx or elsewhere, in order for rheumatic fever to develop.

Certain alternative hypotheses regarding the pathogenesis of rheumatic fever are rendered less tenable by the results of the present investigation. If "autoantibodies" were involved,31 eradication of the streptococcus late in the course of convalescence would hardly be expected to alter the outcome. If a "rheumatogenic toxin" were involved,32 one would expect that it would have been produced during the first few days of illness and that delayed antibacterial therapy would be ineffective. The concept that rheumatic fever begins as a disease entity during the acute streptococcal infection, only becoming clinically manifest two or three weeks later, is not supported by these data, since the streptococcal illness was allowed to progress without interference until a time when the rheumatic process should have already been initiated.

There is some evidence 19,33 to support the hypothesis that rheumatic fever is the pathologic result of a hypersensitivity reaction involving streptococcal antigens. The development of a state of "bacterial allergy" or "hypersensitivity" to bacterial antigens has been demonstrated following infections with numerous bacteria, including streptococci.34 This hypersensitivity, which is of the "delayed" or tuberculin type and is not obviously related to the presence or titer of circulating antibody,35 appears to depend, in general, on the gradual liberation of small quantities of the antigen involved. Thus the intradermal injection of non-hemolytic streptococci is followed by the development of tuberculin type hypersensitivity, while the intravenous injection of these organisms results in the development of a high titer of circulating antibody, but fails to produce delayed hypersensitivity.36 It is possible that during the acute and convalescent phases of streptococcal pharyngitis some antigenic product of the living streptococcus is produced continuously and stimulates the development, over a period of days or weeks, of delayed hypersensitivity. Interference with the production of this material, by eradication of the streptococci even as late as the ninth day of illness, might be expected to prevent the development of hypersensitiveness of sufficiently high degree to elicit rheumatic fever. Alternatively, the rheumatic process might depend on a hypersensitivity reaction involving a product of streptococci, in which case eradication of the organism would eliminate an essential reactant and prevent rheumatic fever.

SUMMARY

Rheumatic fever was prevented when penicillin therapy of streptococcal pharyngitis was delayed until nine days after the onset of illness. Such delayed therapy resulted in eradication of the streptococci from the nasopharynx but did not significantly affect the antistreptolysin response. The data strongly suggest that the development of rheumatic fever requires the presence of living streptococci throughout convalescence. This conclusion is in conflict with certain of the hypotheses previously advanced to explain the pathogenesis of rheumatic fever but may be in accord with the concept that hypersensitivity of the tuberculin or "delayed" type is involved.

Treatment of acute streptococcal pharyngitis with sulfadiazine resulted in only temporary suppression of the streptococci in the nasopharynx and was entirely ineffective in prevention of rheumatic fever.

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The Use of Antibiotics for the Prevention of Rheumatic Fever*

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исн can now be done to prevent rheumatic fever. The group A streptococcus has been firmly established as the inciting agent both of first attacks and recurrences of the disease.1-4 The intelligent and judicious employment of chemotherapeutic agents should make rheumatic fever prophylaxis feasible and practical. The efficiency of such prophylaxis depends upon an intimate knowledge of the relationship of the streptococcus to the natural history of rheumatic fever and upon a thorough understanding of the principles of the chemotherapy and chemoprophylaxis of streptococcal infections. It is our purpose to review some of these principles and to evaluate several methods which have been used successfully to reduce the incidence and morbidity of the disease.

There are two effective approaches to the prevention of rheumatic fever by the use of antibiotics. The first is protection of the highly susceptible rheumatic subject from repeated attacks of the disease by maintaining continuous chemoprophylaxis against new streptococcal infections. The second is prompt and adequate treatment of streptococcal pharyngitis in the general population to reduce the incidence of first attacks of rheumatic fever. Each approach is based upon somewhat different considerations and will therefore be discussed separately.

PREVENTION OF RECURRENCES OF RHEUMATIC FEVER

Background. The risk of recurrent attacks of rheumatic fever to the patient who has recovered from an initial bout of the disease is great. From 60 to 75 per cent of patients who had one episode of rheumatic fever suffered recurrences in the period prior to widespread employment of antibiotics. The recurrence rates in 239 rheu-

matic subjects followed for an average period of seven years at the Babies' and the Presbyterian Hospitals in New York City are shown in Table 1; these patients suffered their initial attack in the years between 1932 and 1940. From these and other data it is apparent that the greatest num-

TABLE I
RECURRENCES OF RHEUMATIC FEVER*

Recurrences	Total	Years after onset							
	Total	1	2	3	4	5	6	7	8+
First	116	43	32	17	6	6	5	4	3
Second	44		10	17	5	5	2	1	3
Third	17					1	4	1	1
Additional	16				3	4	5	4	
Total	193	43	42	40	18	16	16	10	7

* Frequency of recurrences of rheumatic fever in 239 patients followed for year or more (mean seven years) at Presbyterian Hospital and Babies Hospital (onset 1932–1940). (From: E. E. Fischel, unpublished data.)

ber of recurrences occur in the first three years following an episode of rheumatic fever. Thereafter the rate of recurrence falls off sharply, approaching a rather constant value after the fourth and fifth year.

It has been possible to demonstrate serologic evidence of a recent streptococcal infection in almost every patient with acute rheumatic fever.^{6,7} The probability of detecting such evidence increases with the number of specific streptococcal antibodies measured.⁶ When recurrences of rheumatic fever are studied by careful immunologic technics, recent streptococcal infection can be demonstrated almost invariably.

Five hundred eighty patients were observed at

^{*} From the Irvington House and the Department of Medicine, New York University College of Medicine, New York, N. Y.

Irvington House during the first year of recovery from an attack of rheumatic fever. To detect evidence of new streptococcal infection during the period of observation throat cultures were made at regular intervals and serum titers of antistreptolysin O, antistreptokinase and anti-

DELAYED APPEARANCE OF RHEUMATIC HEART DISEASE

Fig. 1. Bland and Jones (Circulation, 4: 836, 1951).

hyaluronidase were determined serially. After the acute rheumatic process appeared to have had subsided completely for a period of at least two months, no new attacks of rheumatic fever were observed in the absence of bacteriologic or immunologic evidence of new streptococcal infection. Serologic or bacteriologic evidence of intercurrent streptococcal infection was demonstrable in all of seventeen rheumatic recurrences studied in this series.⁸

It would appear that acute rheumatic fever, once completely quiescent, rarely exacerbates if subsequent streptococcal infection can be prevented. In the chronic phase, however, the rheumatic process may continue to smoulder for long periods without additional streptococcal exposure. It remains for future long-term studies to determine to what extent antistreptococcal prophylaxis will alter the natural history of rheumatic heart disease. Will valvular sclerosis progress inexorably in the absence of frank or subclinical exacerbations of the rheumatic process associated with new streptococcal infections? Will patients who recover from episodes of acute rheumatic fever without apparent cardiac damage develop valvular lesions several years later if new streptococcal exposures are forestalled?

A study made in the era before the use of antibiotics⁹ showed that in almost half of the patients who recovered from an attack of rheumatic fever without apparent cardiac damage rheumatic heart disease subsequently developed. In most cases such lesions appeared without knowledge of new rheumatic attacks. (Fig. 1.) At the present time about two-thirds of patients

treated at Irvington House recover from an initial attack of rheumatic fever without evident cardiac damage. Careful prophylaxis maintained over a period of years and detailed immunologic studies to detect subclinical intercurrent strepto-coccal infection should determine whether the delayed appearance of rheumatic heart disease can be prevented. Preliminary observations made for a period of three years have been encouraging 10 but do not yet provide conclusive answers.

The data of Bland and Jones also indicate that about one-third of the group of patients who sustained cardiac damage following an attack of rheumatic fever ultimately healed completely or showed improvement in cardiac status during the twenty-year study. It is conceivable that the prognosis for the young rheumatic cardiac also might be improved by continuous chemoprophylaxis. Indeed, the consequences of recurrences in this group must be considered particularly grave. The longevity of the rheumatic cardiac may depend to a considerable extent upon his protection from renewed bouts of carditis. Unfortunately, there is as yet no known way to terminate those attacks of rheumatic fever which enter a chronic phase and result in severe cardiac damage despite complete protection from intercurrent streptococcal infection.

General Principles. Despite the rudimentary state of knowledge of the pathogenesis of rheumatic fever, some general principles have been formulated for the prevention of recurrences.11 The attack rate of rheumatic fever in the general population following streptococcal pharyngitis has been estimated to be about 3 per cent.12 In patients who have suffered a recent bout of rheumatic fever this attack rate has been reported as high as 50 per cent.13 From serologic and bacteriologic studies it is known that subclinical streptococcal infections are frequent and can initiate new attacks of rheumatic fever.6-8 It is generally agreed, therefore, that the highly susceptible rheumatic subject must be continuously protected against streptococcal exposure and that for such patients it is unsafe to await clinical signs of upper respiratory infection before initiating antibiotic prophylaxis.

The decision as to how long prophylaxis must be maintained is a matter to be determined by individual circumstances. Certainly it would seem wise to protect the rheumatic fever patient for at least the five-year period following a rheumatic attack during which the recurrence rate is known to be highest. This period should be extended for the young rheumatic subject. It would be unwise to discontinue protection if after five years the patient is still of elementary or secondary school age, the period of highest incidence of streptococcal infections. Similarly, prophylaxis may have to be maintained longer if the rheumatic subject attains the age of eighteen but is exposed to an environment in which the risk of streptococcal exposure is high. This is particularly true when rheumatic heart disease is present.

Limited data are available upon which to base recommendations for the adult rheumatic cardiac. The frequency of streptococcal infection and rheumatic recurrences in this age group is not well documented. It is known, however, that rheumatic recurrences may occur at any age and it is well to weigh the possible disastrous consequences of a new attack of rheumatic fever in a patient with severe rheumatic heart disease against the expense and inconvenience of maintaining such patients upon antibiotics continuously. It has been recommended that all patients with rheumatic heart disease on the wards of general hospitals receive chemoprophylaxis against streptococcal exposure. 14 Extension of such protection beyond the hospital environment appears reasonable.

It is not yet known whether the attack rate of rheumatic fever following streptococcal infection will be diminished after continuous prophylaxis is maintained for several years. Until more information becomes available as to whether susceptibility to rheumatic attacks "wears off" with periods of freedom from streptococcal infection, it is difficult to limit the duration of continuous prophylaxis arbitrarily.

The selection of patients for continuous chemoprophylaxis should logically include all who have had a recent well defined attack of rheumatic fever. This selection cannot be made solely on the basis of age, severity of the attack or limitation of the overt disease process to the joints or central nervous system. The disease is recurrent in the older as well as the younger age group. An initial mild attack may be followed by a second bout of severe crippling, even fatal carditis. A rheumatic career beginning with Sydenham's chorea may end with advanced rheumatic heart disease.

Patients whose clinical manifestations meet the diagnostic criteria of Jones¹⁵ present no problem of selection. The frequency with which rheumatic fever begins as an ill defined clinical syndrome, however, imposes an important limitation upon this method of prophylaxis. The decision to start prophylaxis for a period of years is a serious one and involves the possibility of causing psychic trauma and even invalidism

TABLE II

EFFECT OF SULFONAMIDE PROPHYLAXIS ON RECURRENCE OF
RHEUMATIC FEVER*

_1 1	Patient Seasons	Rheumatic Attacks		
	Scasons	No.	Percentage	
Control	1,697 1,358	283 27	14.0 1.9	

^{*} Data include references 16-26, inclusive, as summarized by Rammelkamp.⁶⁹

unnecessarily in individuals who are not really rheumatic. At the risk of failing to recognize some rheumatic subjects, it is best to reserve prophylaxis for those whose diagnosis is firmly established. Before instituting small prophylactic doses of antibiotic to prevent new streptococcal infection, it has been considered advisable to administer a course of penicillin therapy adequate to eradicate the streptococcal carrier state as soon as the diagnosis of rheumatic fever has been made.11 The absence of clinical signs of pharyngitis and the failure to culture group A streptococci from the nose or throat may not always exclude the presence of these organisms deeper in the tissues, particularly in the presence of enlarged tonsils.

The peak incidence of rheumatic fever in the United States usually occurs in the spring; the lowest point in the late fall. Sporadic and even epidemic streptococcal infection can occur at any season, however, so that prophylaxis should be maintained throughout the year.

Methods. Many antibiotics are now available which are effective against group A streptococci. This discussion is limited to those methods which have been applied most extensively to the prevention of rheumatic fever.

Sulfonamide prophylaxis: Fifteen years have elapsed since the first reports of Coburn and Moore, 16 and Thomas and France 17 suggested that the incidence of recurrent attacks of rheumatic fever could be reduced by continuous

prophylaxis with sulfonamides. Since then many independent studies and a vast military experience during World War II^{18–28} have provided a wealth of data which permit some definite conclusions. Some of the data have been summarized in several recent reviews. ^{1,4,29,30} The

tively high.²⁹ This has not been noted in subsequent studies on large numbers of rheumatic patients,^{26,28} particularly when small doses of sulfadiazine rather than sulfanilamide have been employed.

Fatal agranulocytosis has occurred when pa-

TABLE III
EFFECT OF ORAL PENICILLIN PROPHYLAXIS ON RECURRENCE OF RHEUMATIC FEVER

		Trea	ted Group	Control Group	
Reference	Dose of Penicillin	Patient Years	Recurrences	Patient Years	Recurrences
Maliner, Amsterdam ³⁵	1,000-5,000 u. t.i.d. (troches)	44	0	44	4
Maliner ³⁶		33	0	30	2
Hofer ³⁹	100,000 u. b.i.d.	108	0	110	0
Smith, Skinner, Erickson 70	100,000 to 200,000 u. t.i.d.	36	0	36	0
Brick et al. 40	50,000 u. b.i.d.	76	3	76	6
Evans ³⁸		310	0	290	4
Kohn, Milzer, Maclean 42	800,000 u. daily*	48	0	125	20
		45	1	115	16
		40	1	106	19
Total		740	5	932	81
Per cent recurrences per patient yea	r		0.6		8.7

^{*} This dose was administered for the first week of each month nine months of the year (spring, autumn and winter). Results of the first two years of this five-year study are not included because the penicillin regimen was varied and not consistently maintained.

combined experience indicates that sulfonamide prophylaxis reduces the incidence of recurrences of rheumatic fever by at least 85 per cent. (Table II.)

In addition to proven effectiveness, sulfadiazine has the advantages of being easy to administer, relatively inexpensive and of low toxicity. Some of the newer sulfonamides such as gantrisin® are probably equally effective³¹ but offer no practical advantage. The dose of sulfadiazine recommended is 1.0 gm. daily, given either as a single dose or in divided doses of 0.5 gm. twice daily. The single dose is often preferred to reduce the hazard of forgetfulness.

Serious toxic reactions to such small doses of sulfadiazine are uncommon. In mass prophylaxis studies such reactions, usually granulocytopenia or exfoliative dermatitis, occurred in approximately one in 10,000 subjects. Mild toxic reactions, such as transient dermatitis, were noted in 0.5 per cent of subjects.²⁷ In some earlier studies the incidence of toxic reactions to sulfanilamide in rheumatic subjects was reported to be rela-

tients receiving sulfonamides prophylactically developed unnoticed, mild granulocytopenia and were subsequently given additional, larger doses of sulfonamide to combat an intercurrent infection.²⁷ A different antibiotic should be chosen to treat such superinfections.

Group A streptococci resistant to sulfonamides have been encountered in large scale prophylactic programs in military groups. ²⁷ Such resistant strains have appeared only occasionally in civilian life. ^{32,33} These do not constitute a serious threat because of the wide variety of effective antibiotics available. On two occasions an epidemic of sulfonamide-resistant infection developed in a convalescent home housing many rheumatic children. Prophylaxis was changed to oral penicillin in doses of 100,000 units twice daily, which prevented further outbreaks. ³⁴

A major limitation of sulfonamides is inherent in their mode of chemotherapeutic action. As bacteriostatic rather than bactericidal agents, their action is suppressive only. They do not eradicate the streptococcal carrier state. They are useful,

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therefore, primarily in preventing new streptococcal infection after streptococci have been eradicated by other means.

Penicillin prophylaxis: The striking effectiveness of penicillin against group A streptococci and the limitations of sulfonamide prophylaxis have encouraged many recent studies of penicillin prophylaxis of rheumatic fever.

In some of the earlier reports penicillin troches were used in a small series of patients and rheumatic recurrences were not observed. 35,36 Varying doses of penicillin have been administered orally with favorable results. 37-42 Several controlled studies on limited numbers of patients indicate a marked reduction in recurrence rates. (Table III.) Massell has found that the administration of 100,000 to 200,000 units of penicillin orally three times daily has prevented streptococcal respiratory infections and recurrences of rheumatic fever in a group of patients at the House of the Good Samaritan during a five-year period. 43

It is of considerable theoretic interest that in the studies of Kohn, Milzer and MacLean penicillin prophylaxis was administered intermittently, in doses of 800,000 units daily for the first week of each month, with favorable results. ⁴² As will be emphasized subsequently, such large doses given over this period of time are probably sufficient to eradicate the streptococcal carrier state in most instances. The results imply that under these conditions there may be a "safe" interval of three weeks between courses of penicillin before rheumatic fever can be reactivated. Until more information is available on this point it is perhaps safer to maintain daily oral penicillin prophylaxis continuously with smaller doses.

It has been determined that oral doses of 500,-000 to 1,000,000 units daily are highly effective, when administered for at least ten days, in achieving clinical cure of streptococcal pharyngitis and in eradicating the carrier state. 44,45 It is quite reasonable to assume that continuous daily oral prophylaxis with penicillin in the rheumatic patient would not require a larger dose than this, even under epidemic conditions.

Highly significant, controlled data concerning the effectiveness of small daily oral doses of penicillin in preventing streptococcal infections are accumulating rapidly from studies in progress in the Armed Forces. Mass prophylaxis undertaken during epidemics of streptococcal respiratory infections in naval recruits indicate that single daily oral doses of 50,000 units to 100,000 units are effective in preventing strepto-coccal infection. 45,46 Such small doses are not adequate to treat the infected patient, however, and do not eradicate the carrier state. They are probably not entirely adequate for absolute protection of the individual against streptococcal infection under conditions of high risk. It is not yet known whether such small doses will protect the highly susceptible juvenile rheumatic subject from recurrences of rheumatic fever. Temporarily, it might be safer to employ daily doses of at least 200,000 to 300,000 units.

Reviews of the literature have not revealed a proved instance of penicillin-resistant group A streptococci associated with human infection. From in vitro studies it appears quite unlikely that the group A streptococcus can acquire significant resistance to this antibiotic under the clinical conditions which prevail when penicillin is employed for chemotherapy or chemoprophylaxis. 47 "Penicillin-resistant beta hemolytic streptococci" which were reported to have been isolated from patients receiving penicillin prophylaxis were subsequently identified as belonging to serologic groups other than "A."42 There is no evidence from the studies of mass prophylaxis in the Armed Forces that the widespread use of penicillin prophylaxis is giving rise to any change in the sensitivity of group A streptococci to penicillin.45

Toxic reactions to small oral doses of penicillin occur rarely and when present are usually mild. The incidence of such reactions in mass prophylaxis studies involving many thousand troops was about 0.3 to 0.7 per cent. 45,46,48 Well controlled data concerning the true incidence of penicillin reactions are scarce. In a recent study placebos of sodium bicarbonate were administered to 1,762 men. Three (0.2 per cent) were diagnosed as having "penicillin reactions" by medical officers who were unaware of the placebo treatment. 46

Urticaria, which occasionally develops during the administration of oral penicillin, is usually transient. If penicillin is discontinued for a few days it can be restarted in most instances without causing further reactions. 49 When reactions are more severe and associated with angioneurotic edema, penicillin should be permanently discontinued. Even these reactions, however, do not necessarily indicate permanent sensitization to penicillin.

It is usually recommended that penicillin be

administered orally under fasting conditions to assure optimum absorption. In a recent controlled study which was conducted on a limited number of subjects, administration of penicillin tablets buffered with sodium citrate resulted in good absorption irrespective of whether they were taken before or after meals. 50 This observation, if confirmed, is of importance since many patients cannot be relied upon to take medication regularly half an hour before breakfast.

Repository penicillin (benzathine penicillin): The major disadvantage of daily oral prophylactic medication is that ambulatory patients are apt to forget to take the tablets regularly. Recently a new repository penicillin compound, benzathine penicillin (N,N' dibenzylethylenediamine dipenicillin G), has been developed. The injection of 600,000 units of this compound provides low serum levels of penicillin for twelve to fourteen days. A single injection of 1.2 million units results in detectable penicillin serum levels for three to four weeks.⁵¹

During a ten-month study benzathine penicillin was administered either once or twice monthly to a group of 143 hospitalized patients and was found to be effective in eradicating the streptococcal carrier state and preventing rheumatic recurrences.⁵¹ A subsequent study was made of the administration of 1.2 million units of this compound every four weeks to 145 outpatients recently recovered from rheumatic fever. During a twenty-one-month period no rheumatic recurrences were observed in this group. Of 2,716 throat cultures made routinely, three were positive for group A streptococci. A significant rise in antistreptolysin O titers, which were determined in all patients monthly, was noted in but three instances. 10,52

Similar results were obtained in an independent study of ninety-six rheumatic fever patients who received 1.2 million units of benzathine penicillin monthly during a period of fourteen months. No recurrences were observed. Of 1,045 throat cultures four were positive for group A streptococci and only two patients had a significant rise in serum titer of antistreptolysin O.53

The site of injection tends to be more painful with the use of this compound than with procaine penicillin. Severe local reactions resulting in abscess formation have not been observed. Mild, transient fever may accompany the local reaction. Hypersensitivity reactions to benzathine penicillin so far have not been more frequent or

more severe than those observed with the parenteral use of other forms of penicillin. During the past three years 6,624 injections have been administered to 553 rheumatic fever patients on the wards and in the outpatient clinic at Irvington House for period ranging from ten to twentyone months. Six patients developed transient urticaria which lasted for three to four days and subsided despite persistence of penicillin in the blood for several weeks thereafter. Continued treatment with the same compound did not result in further reactions. One patient developed angioneurotic edema, and penicillin was permanently withdrawn although the reaction lasted but a few days. Eight patients developed nonspecific rashes which were evanescent, did not recur with continued therapy, and could not be definitely attributed to penicillin allergy.

In another study of ninety-six children who received 1,000 injections of benzathine penicillin during a period of fourteen months there were two reactions. One patient developed urticaria which lasted four days and one had transient polyarthralgia. Neither reaction reappeared when treatment was continued.⁵³ No hypersensitivity reactions to single injections of benzathine penicillin were noted in one group of 108 children treated for streptococcal pharyngitis⁵⁴ or in a group of sixty-one children to whom this compound was administered as prophylaxis against suppurative complications of measles.⁵⁵

In a careful study of 257 adults who were treated for streptococcal pharyngitis with a single injection of either 1.2 million units or 600,000 units of benzathine penicillin G, there were six illnesses (2.3 per cent) which could be considered complications of penicillin therapy. A comparable group of patients receiving other forms of penicillin parenterally was not included.⁵⁶

Carefully controlled studies on the relative frequency of toxic reactions to various types of penicillin administered parenterally are not available. So far it would appear that the parenteral use of benzathine penicillin has not been attended by a higher incidence of hypersensitivity than has been encountered with the parenteral use of other penicillin compounds.

In the absence of controlled observations it is difficult to determine whether hypersensitivity reactions are less frequent when comparable doses of penicillin are administered orally. In one large series the incidence of penicillin reactions to large oral doses of penicillin administered for ten days was 1 to 2 per cent.⁴⁴

It has been shown that the use of oral doses of penicillin⁶⁴ or of monthly injections of benzathine penicillin⁵¹ does not increase significantly the penicillin resistance of pharyngeal strains of

reliability, is relatively economical and, though somewhat painful, appears so far to be safe.

The choice of one of the three types of prophylactic medication discussed in the preceding paragraphs varies according to individual considerations. Some patients can be relied upon

TABLE IV
METHODS OF CONTINUOUS CHEMOPROPHYLAXIS

Antibiotics	Advantages	Disadvantages	Recommended Dose	Toxicity
Sulfadiazine	Easily administered Well absorbed Inexpensive Established effectiveness	Frequent breaks in routine Risk of serious toxicity Resistant streptococci Bacteriostatic	1.0 gm./day	Skin eruptions—0.5% Blood reactions—0.01%
Oral penicillin	2. Serious toxicity rare 2. Irregular absorption once or twice dail		200,000-250,000 units once or twice daily	Urticaria; angioneurosis 0.3-0.7% "serum type sickness"
Oran penkinin	3. No resident surproceed	Minimum effective dose not well established		Anaphylaxis "Periarteritis" rare
Repository benzathine penicillin	"Break" in prophylaxis less likely Single dose usually eliminates carrier state Economical Close patient contact Other advantages of penicillin (See oral penicillin)	Requires injection Moderate local soreness	1,200,000 units I.M. once monthly	Urticaria Angioneurosis "Serum type sickness" Anaphylaxis "Periarteritis"

Streptococcus viridans. Serum levels of penicillin following injection of benzathine penicillin remain very low and although effective against such exquisitely sensitive organisms as group A streptococci and gonococci, such low levels of penicillin do not protect against the less sensitive green streptococcus. Two patients have developed subacute bacterial endocarditis while receiving monthly injections of benzathine penicillin as prophylaxis against rheumatic recurrences. In both instances the organisms recovered were penicillin sensitive and both patients were cured by large doses of penicillin G (2.5 to 10 million units daily) given for four weeks. 10

In addition, the low penicillin blood levels which result from intramuscular injection of benzathine penicillin are not adequate for prophylaxis or treatment of many strains of Staphylococcus aureus. Because of these low blood levels, however, the penicillin resistance of Staph. aureus cannot be greatly increased by the prolonged administration of benzathine penicillin. Under these circumstances superinfection with this organism has been cured by daily doses of 600,000 units of aqueous procaine penicillin given intramuscularly for seven days. 10

Administration of single monthly injections of benzathine penicillin as continuous prophylaxis for rheumatic subjects has the advantage of to take tablets daily without fail. Others may consider it safer and easier to come to the doctor's office or clinic once a month for an injection of benzathine penicillin. A brief comparison of the three methods of continuous prophylaxis appears in Table IV.

Other antibiotics such as aureomycin, terramycin or tetracycline probably can be employed successfully to prevent rheumatic recurrences. At present, however, such compounds offer no significant advantages, are more costly and should be reserved for patients intolerant of penicillin or sulfonamides.

PREVENTION OF INITIAL ATTACKS OF RHEUMATIC FEVER

If streptococcal infections are treated promptly and adequately with penicillin the frequency with which rheumatic fever develops subsequently can be greatly reduced. Studies conducted at the House of the Good Samaritan first indicated that early treatment of streptococcal infections with intensive penicillin therapy prevents recurrent attacks of rheumatic fever in rheumatic subjects. 57-59 Since then admirably controlled large scale studies conducted at the Streptococcus Disease Laboratory at Francis E. Warren Air Force Base have extended these

observations to include the general population and have established firmly the chemotherapeutic principles upon which such prevention is based. 60-61 These studies indicate that the incidence of *overt* rheumatic fever can be reduced by 96 per cent in patients properly treated with

onset of symptoms may still exert some favorable prophylactic effect upon the incidence of rheumatic sequelae. 62

Complete eradication of streptococci from the throat during therapy is essential. Sulfonamides, which are bacteriostatic rather than bactericidal

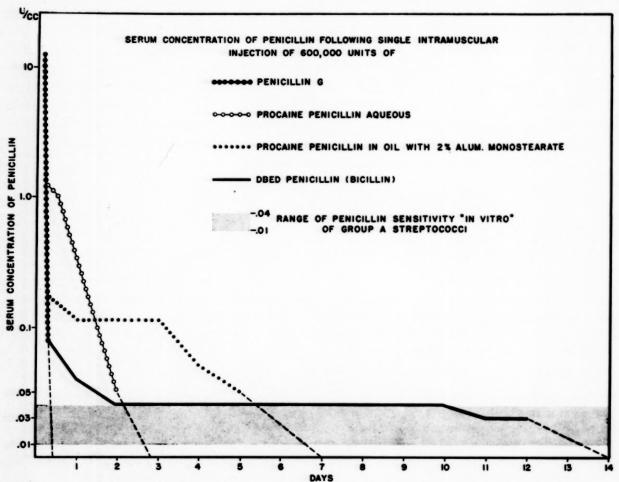


Fig. 2. Penicillin blood levels. Published through the courtesy of American Practitioner and Digest of Treatment. 66

penicillin but it has not yet been proven that subclinical rheumatic carditis has been averted. It would appear reasonable, however, to accept for the present a method which has been shown to prevent at least the frank clinical manifestations of rheumatic fever which follow streptococcal infection.

The earlier penicillin is instituted in the course of streptococcal pharyngitis the more effective is prevention of subsequent rheumatic fever. Optimum results are obtained when treatment is initiated within forty-eight hours of the onset of symptoms of sore throat. There is some recent evidence to suggest, however, that treatment instituted even as late as nine days after the

agents, have long been known to be ineffective in this regard.⁶³ Penicillin, although a powerful bactericidal agent against group A streptococci, must be administered well beyond the period of clinical cure to remove these organisms from the throat completely.

Group A streptococci are exquisitely sensitive to penicillin (almost invariably less than 0.04 units per ml. in vitro). The blood concentration of penicillin need not be high to achieve a maximum killing effect. Once such levels have been provided, efficiency of chemotherapy is a function of its duration. These experimental principles have found empirical confirmation in studies which have established the dose

schedules of penicillin required to eradicate permanently the streptococcal carrier state. 44,45

If penicillin is administered orally, a minimum daily dose of 500,000 units must be given for ten days. Larger doses given for shorter periods are less effective. If penicillin is administered parenterally any schedule may be employed which maintains effective concentrations of penicillin for a ten day period. Thus daily injections of 300,000 units of procaine penicillin for ten days; 600,000 units of procaine penicillin in oil with 2 per cent aluminum monostearate given every other day for three or four doses; or one injection of 600,000 to 1.2 million units of benzathine penicillin⁵⁶ have proven highly effective. The average serum levels resulting from a single injection of different forms of repository penicillin are shown in Figure 2.66

The practical advantage of administering a single injection suggests that benzathine penicillin is the treatment of choice for streptococcal pharyngitis if subsequent, more extensive experience confirms the low incidence of penicillin hypersensitivity. If the oral route of administration is chosen, treatment must be maintained for a minimum period of ten days. This regimen is often difficult to enforce because clinical symptoms of streptococcal sore throat almost always abate within twenty-four to forty-eight hours when penicillin is administered. In younger children vomiting often accompanies streptococcal sore throat, which makes oral therapy unreliable.

Treatment of streptococcal infection with aureomycin also reduces the incidence of rheumatic sequelae. It is somewhat less effective than penicillin. ⁶⁷ The dose of aureomycin recommended is 2 gm. daily for seven days. Its use is preferred for patients who are sensitive to penicillin.

It is quite apparent that the major limitation of the chemotherapeutic approach to the prevention of rheumatic fever is the difficulty of clinical identification of streptococcal sore throat. To avoid the promiscuous and unnecessary administration of penicillin to patients with viral and non-streptococcal upper respiratory infections, the clinical criteria for the diagnosis of streptococcal pharyngitis should be more widely recognized. Simple coryza, cough, hoarseness and tracheitis are rarely due to streptococci. The syndrome of sudden onset of fever, sore throat, "beefy" redness of the pharynx, and pharyngeal exudate suggests the diagnosis.

Cervical lymphadenitis and the presence of leukocytosis add further evidence for it. In a recent large series of patients studied a proper diagnosis was made on clinical criteria alone with 70 per cent accuracy.⁶⁸

Because the preceding streptococcal infection may be inapparent in at least 38 per cent of patients in whom rheumatic fever develops⁶⁹ it is obvious that the chemotherapeutic approach will prevent, at best, little more than half of the total cases. The proper diagnosis, treatment and control of streptococcal infections may reduce their prevalence and this could be reflected in a further decline in the incidence of rheumatic fever.

The use of antibiotics in the prophylaxis of rheumatic fever is far from an ideal solution of the problem. Pending more knowledge and a better approach, however, the incidence and morbidity of the disease can be reduced significantly by appreciation on the part of physicians and the general public of the importance of early diagnosis and proper therapy of streptococcal disease and upon diligent protection of rheumatic subjects from streptococcal infection.

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Laboratory Aids in the Diagnosis of Rheumatic Fever and in Evaluation of Disease Activity*

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THERE are two ways in which the laboratory might be expected to give assistance in dealing with the problem of rheumatic fever. The first is in the diagnosis of the disease, and the second is in guiding the medical management of the disease by providing an index of rheumatic activity. At the present time completely satisfactory laboratory procedures have not been developed in either of these categories. Thus there is still no specific diagnostic test for rheumatic fever, and there is no test for rheumatic activity that can be relied upon when the patient is under full therapy. However, there are laboratory procedures available which, despite their limitations, can be of great value both in diagnosis and management of the disease. The purpose of this paper is to emphasize the most practical and generally applicable of these procedures and to consider their interpretation and evaluation.

The classic and readily recognized cases of acute rheumatic fever represent only a portion of the total cases, and diagnosis frequently presents a difficult clinical problem in the others. Because of the diversity of the manifestations of the disease and the variability of the combinations in which they can occur, it is not possible to apply any simple formula in arriving at a diagnosis. The large number of disease entities that have been confused with rheumatic fever and that must be considered in differential diagnosis emphasize the diagnostic difficulties. It is evident that in a situation of this kind a specific diagnostic test would be of inestimable value. It is not necessary that such a test be based upon a thorough understanding of the pathogenetic mechanisms in rheumatic fever, a fact that is adequately demonstrated by such procedures as

the Wassermann test for syphilis and the heterophile antibody test as employed in the diagnosis of infectious mononucleosis. However, up to the present time a procedure of this type has not been developed to assist in the diagnosis of rheumatic fever.

In the absence of a specific test for rheumatic fever the laboratory is still able to make an important contribution by supplying evidence concerning the occurrence of recent streptococcal infections. During the past few decades the relationship between group A streptococcal infections, usually streptococcal pharyngitis or tonsillitis, and rheumatic fever has become firmly established. The time relationships between the precursory bacterial infection and the onset of the rheumatic attack have been clearly defined, and the pattern is sufficiently reproducible to provide a basis for diagnostic procedures. The bacteriologic isolation and identification of group A streptococci is of only limited value in this regard. Due to the fact that a period of several days to several weeks intervenes between the acute bacterial infection and the onset of rheumatic fever, the offending organisms are frequently not recoverable after rheumatic symptoms have appeared. This has become increasingly true with the introduction of penicillin and other antibacterial agents, since one of these drugs has often been administered at some time during the prodromal period of the disease. Furthermore, the successful isolation of group A streptococci may give no information about the time of occurrence of an acute infection, because the carrier state can persist for an indefinite

The demonstration of serum antibodies to individual antigens of group A streptococci has

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proved to be a much more valuable tool for detecting the occurrence of recent streptococcal infections. While the pattern of the antibody response to a number of different streptococcal components has been studied in detail, the antibodies to certain of the biologically active extracellular products of group A streptococci have received most attention. In general, the appearance and disappearance of antibody follows the same course in the case of each of these antigens. A rise in antibody titer becomes detectable in the second week following the streptococcal infection and the titer increases until a maximum level is reached at four to six weeks. Subsequently, the titer remains at or about the maximum level for a variable period and then gradually declines at a rate that is considerably slower than the rate of initial increase of antibody. These facts are of importance in interpretation of the results of antibody studies in rheumatic fever, since it is necessary to take into consideration the duration of the disease and the probable interval that has elapsed since the streptococcal infection. The so-called latent period between the streptococcal infection and the onset of rheumatic fever is usually shorter than the time required to reach maximum antibody titer, consequently the titer is still increasing during the early phase of the illness. This is of importance in some instances, since the first serum drawn may contain insufficient antibody to establish the occurrence of a recent streptococcal infection, while serum obtained one to two weeks later may show a greatly increased titer. On the other hand, if the patient first comes under observation some months after the onset of rheumatic disease the titer of antibody may have fallen again to a range of uncertain significance. These examples serve to illustrate the fact that the numerical expression of the antibody titer supplied to the clinician by the laboratory does not stand by itself but must be interpreted in the light of the complete clinical picture.

Of the several antibody determinations that have been studied in connection with rheumatic fever, the one that is most practical and feasible as a routine diagnostic tool is the antistreptolysin O test. This test possesses numerous advantages over other available antibody titrations. Not only is the test itself simple to carry out but also the reagents are more readily available than is the case with the tests for other antibodies. The latter is particularly true now that the antigen,

streptolysin O, is available commercially;* but even if the antigen is prepared in the laboratory the antistreptolysin O determination requires the least in the way of special materials. In the case of the antibody to streptokinase the test employs a complex reaction mixture made up of materials that are not readily standardized or freed of substances that may interfere with the test. The procedure for estimation of antibody to streptococcal hyaluronidase is relatively simple but it depends on the use of highly polymerized hyaluronic acid as substrate and this material is not conveniently prepared in large amounts. Similarly, the test for antidesoxyribonuclease depends on the availability of high molecular desoxyribonucleic acid, and in addition the use of this test suffers from a more serious drawback in that a much smaller proportion of patients respond to this antigen following streptococcal infections than is the case with the other antigens mentioned. Since the antistreptolysin O determination requires nothing more complicated as substrate than washed rabbit red blood cells, it will be readily understood why it has become the most widely used procedure for demonstrating the occurrence of recent streptococcal infection.

A number of modifications of Todd's original procedure for titrating serum antistreptolysin O have been devised but the differences are primarily in the method of preparing the serum dilutions. The end-point of the titrations by all these procedures is the highest dilution of serum that completely inhibits lysis of red cells by one unit of streptolysin O, and the results are frequently expressed numerically as the reciprocal of this dilution. Thus a serum that prevents lysis at a dilution of 1:500 is said to contain 500 units of antistreptolysin O. Modifications of the dilution method have been designed to reduce the manipulations required and at the same time retain sufficiently narrow dilution increments so that small changes in titer will be detectable.

It is obvious that if the results of the antistreptolysin test are to have similar values in different laboratories, standardization of the procedure assumes considerable importance. It is necessary that the proportion of various reagents and the conditions under which the test is carried out be the same and, most importantly, that an identical standard unit of streptolysin O be universally adopted. In the past this has been accomplished in individual laboratories by

^{*} Difco Laboratories, Detroit, Mich.

checking the standardization of the lysin preparation used either with human sera of known antistreptolysin titer obtained from other laboratories or with the standard horse antistreptolysin prepared by Todd. That this has worked fairly well is indicated by the fact that a comparable

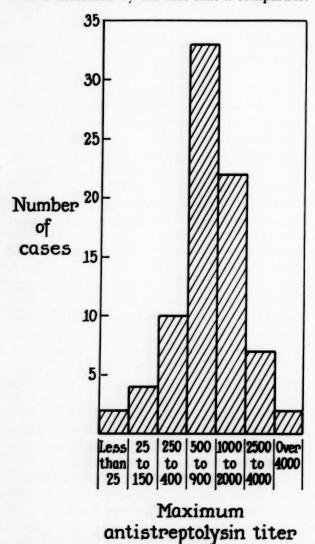


Fig. 1. Distribution of maximal antistreptolysin O titers in eighty consecutive cases of early rheumatic fever.

range of titers in streptococcal disease and rheumatic fever has been reported by different workers. There is, however, no central source of standard antisera, and the problem of biologic standardization remains in a somewhat unsatisfactory state. The maker of commercial streptolysin O attempts to deal with this problem by supplying prestandardized lysin, and if the standardization of the material is carefully controlled, there is no theoretic reason why this should not give reliable results.

If the antistreptolysin test is well controlled,

the results obtained are readily reproducible within the limits imposed by the serial dilution method. Replicate tests rarely vary by more than one tube in the dilution series. It is understandable that many workers have attempted to devise a more quantitative procedure, usually based on colorimetric estimation of hemoglobin released by hemolysis. No quantitative method has yet proved generally acceptable but renewed interest in this problem in several laboratories increases the possibility that a method of this type will be available in the future.

The specificity of the standard antistreptolysin test appears to be very high, and cross-reactions resulting from antibody to similar lysins formed by other bacteria do not present a significant practical problem. In addition, there is adequate evidence that non-streptococcal illnesses do not cause a non-specific rise in the titer of antistreptolysin. The powerful inhibitory effect of certain lipids on streptolysin can be troublesome, however, since changes in serum lipids brought about by bacterial contaminations can result in marked increase in the apparent antistreptolysin content. Thus it is important either to employ procedures to avoid contamination of sera or to carry out titrations while the sera are still fresh.

The use of the antistreptolysin O determination as an adjunct in the diagnosis of rheumatic fever requires a thorough understanding of the behavior of this antibody. It has been demonstrated that at least 80 to 90 per cent of patients with rheumatic fever have definite elevations in antistreptolysin titer early in the course of the disease. This cannot be interpreted as indicating that 10 to 20 per cent of cases of rheumatic fever are not associated with streptococcal disease, since an even larger proportion of patients with proved, uncomplicated streptococcal infections fail to develop this antibody. However, this finding defines one of the limitations of the test as a diagnostic procedure because the absence of a significant rise in the titer of this antibody does not exclude the possibility of a recent streptococcal infection or of rheumatic fever. On the other hand, the antibody response occurs in such a high proportion of cases of rheumatic fever that a low or negligible titer in the early phases of a disease believed to be rheumatic fever should lead to critical re-evaluation of the diagnosis.

The distribution of maximal antistreptolysin O titers in a series of eighty consecutive cases of early acute rheumatic fever studied in the

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Hospital of the Rockefeller Institute is illustrated in Figure 1. It will be noted that the large majority of the cases (seventy-four of eighty, or 92 per cent) have titers of 250 or above. As pointed out in a previous publication, when the same series consisted of forty-six cases, the two cases with maximal titers of less than 25 units were both children under five years of age. There are too few representatives of this young age group in this series to establish the significance of this fact but the finding is consistent with the results of other workers who have found that infants and very young children show a low incidence of antibody response following proved streptococcal infections. 3.4

For all practical purposes, if a single serum specimen shows a titer of 500 units or higher, reasonably good evidence is provided for the occurrence of a recent streptococcal infection. The evidence can be strengthened by repeating the test on later serum specimens to determine whether the titer is rising, falling or stationary. When the titer of the initial serum is lower, e.g. below 500 units, it becomes more imperative to carry out repeated determinations in order to evaluate its possible significance. Thus an initial titer of 250 units would have to be considered an equivocal finding, but a subsequent rise to 500 units followed by a fall during convalescence to levels below the initial titer would clearly indicate that an infection with streptococci had been present not more than a few weeks before the first serum sample was obtained.

The limitations on the diagnostic usefulness of the antistreptolysin O test in rheumatic fever imposed by the fact that not all patients respond with significant increases of antibody to this antigen can be largely overcome in those laboratories that have facilities for carrying out tests for other streptococcal antibodies. An individual who fails to respond to the antigenic stimulus of streptolysin O in the course of a streptococcal infection may respond quite normally to other antigens, such as hyaluronidase or streptokinase. Experience has shown that if a sufficient number of antibodies are studied the proportion of rheumatic fever patients showing an unequivocal response to at least one streptococcal antigen approaches 100 per cent.

A more serious limitation on the diagnostic usefulness of the antistreptolysin O determination derives from the fact that it is in no sense specific for rheumatic fever, and that it is possible for a patient with a disease simulating rheumatic

fever to have a high antistreptolysin O titer as the result of a recent streptococcal infection that is unrelated to the presenting illness. This occurrence will of course be more likely during periods of high endemicity of streptococcal disease or during frank epidemics. In any event, this sequence of events will depend on pure coincidence and will thus be relatively uncommon, but it is well to keep this possibility in mind in evaluating the antistreptolysin O test in individual cases.

The possible effect of antibiotic therapy on the production of streptococcal antibody must be considered in relation to the use of the streptolysin test as a diagnostic procedure. It has been shown in several laboratories that adequate penicillin therapy during acute streptococcal sore throat results in marked suppression of the expected antibody response to a variety of streptococcal antigens. 5-8 However, since this treatment also appears to prevent the occurrence of rheumatic fever,8 this finding has no bearing on the evaluation of the antistreptolysin titer in the diagnosis of rheumatic fever. Antibacterial therapy that is inadequate either in dosage or duration of administration does not consistently eliminate the streptococci from the throat and has little effect on the antibody response or the incidence of rheumatic fever.

By way of summarizing the status of antibody tests as diagnostic tools, it can be stated that the antistreptolysin O test provides a practical procedure which can be successfully carried out in general laboratories and which supplies useful supplementary information in the diagnosis of rheumatic fever.

In addition to the high degree of variability displayed by the symptoms and signs of rheumatic fever, there is an exceedingly broad range in the duration of the disease. Persistent rheumatic activity is frequently subclinical so that it is not readily detected, and for this reason the development of laboratory tests for the estimation of activity of the disease process has been the concern of clinical investigators for many years.

The time-honored test used as an index of rheumatic activity is the determination of the erythrocyte sedimentation rate. This test depends upon changes in the composition of the blood that occur in rheumatic fever, as well as in numerous other diseases, and that result in increased rouleaux formation of the erythrocytes which in turn increases their sedi-

mentability. The erythrocyte sedimentation rate has proved to be of great value in following the course of rheumatic fever and in evaluating therapeutic regimens, and because of its great simplicity and relative reliability there can be little doubt that it will continue to be the most widely used single test for rheumatic activity.

It is not within the scope of this discussion to describe and compare the numerous modifications of the technic of measuring the erythrocyte sedimentation rate. Any of the various well established methods will prove satisfactory if evaluated in terms of the defined normal range and the maximum fall that can be expected. In this laboratory the Westergren method, 9 which has both advantages and disadvantages in comparison with other methods, has been employed for many years. Perhaps one of the most favorable features of this method in its application to rheumatic fever is the fact that the 200 mm. tube provides for a large range between the normal values and the maximum observed during the acute disease. As a result, changes in the sedimentation rate measured by this method are expressed by larger increments and provide a reliable index of the progress of suppressive therapy. In acute rheumatic fever values commonly obtained by this method range from 90 to 130 mm. in the first hour, and the rates for normal individuals are usually below 15 mm./ hour. Successful suppressive therapy is accompanied by a progressive decline in the sedimentation rate, and a failure of the rate to decline or an increase in the rate indicates that the disease process is not being adequately controlled.

Despite the simplicity of the sedimentation test, it has certain deficiencies as a tool for the measurement of rheumatic activity. As evidence for this statement one can cite the continued search for other tests and the variety of procedures that have already been suggested to replace or supplement the sedimentation rate. Among the limitations of the sedimentation rate is the fact that the normal range is somewhat poorly defined so that some healthy individuals show values that fall in what is usually considered the pathologic range. Furthermore, the test often appears to be insensitive. The sedimentation rate may at times respond sluggishly to obvious changes in the clinical condition, and in the presence of low grade activity it may be normal or equivocal. The alternative procedures that have been employed for estimating rheumatic activity include the following: total

leukocyte count, the Weltmann serum coagulation reaction, ¹⁰ determination of serum mucoprotein, ¹¹ measurement of non-specific hyaluronidase inhibitor of serum, ¹² measurement of serum complement, ¹³ determination of serum C-reactive protein, ¹⁴ the bactericidal activity of the blood versus Bacillus subtilis, ¹⁵ a serum precipitation reaction with a quaternary ammonium salt ¹⁶ and a diphenylamine color reaction with serum. ¹⁷

Except for the leukocyte count, which is too insensitive to be of great value, the most widely used of these procedures at the present time is the determination of the presence of C-reactive protein in the serum. 14.18-21 Until recently the use of this test was severely limited by the fact that the reagent required for detection of the protein, specific rabbit antiserum to C-reactive protein, was not readily available. Since the antiserum is now produced commercially* this restriction on the general usefulness of the procedure no longer prevails.

C-reactive protein is a substance that is not present in the blood of normal, healthy subjects but appears promptly in the course of a wide variety of disease states. It owes its name to the fact that its occurrence was first recognized as a result of its property of reacting to form a precipitate with the so-called C polysaccharide of pneumococcus. C-protein is serologically distinct from the normal proteins of serum, and consequently it is possible to use specific antiserum as a reagent for detecting its presence in patients' sera. The technical procedures involved in carrying out the test are exceedingly simple and involve application of the economical capillary precipitin technic first described for use in the grouping and typing of hemolytic streptococci.22 Equal parts of the patient's serum and rabbit antiserum to C-protein are mixed in a capillary tube, and after appropriate incubation and refrigeration the degree of reactivity is determined on the basis of the amount of precipitate in the tube. The procedure is only semi-quantitative but the volume of precipitate formed provides a reasonably accurate index of the amount of C-reactive protein present in the serum.

Except in cases of pure chorea, C-reactive protein is always present in the serum in acute rheumatic fever, and the amount present is more or less proportional to the severity of the illness. There is a rough correlation between the eryth-

^{*} Schieffelin and Co., New York, N. Y.

rocyte sedimentation rate and C-reactive protein but there are many instances in which the results of the two tests are dissimilar. For example, in the early recovery period of rheumatic fever the C-reactive protein usually becomes negative before the sedimentation rate has returned to normal, and in the so-called laboratory rebounds that follow discontinuation of therapy it is not uncommon to encounter a rise in the sedimentation rate unaccompanied by the appearance of C-protein.

One of the advantages of the C-protein test is that normal subjects give completely negative reactions and there is no "normal range" to complicate interpretation. In addition, the test appears to be highly sensitive and changes in the patient's condition are reflected quite promptly, and in some cases predicted by changes in the concentration of C-protein. The test serves as a highly useful adjunct to the erythrocyte sedimentation rate in guiding the medical management of rheumatic fever.

It must be apparent that the various tests for rheumatic activity have but little value as diagnostic tools since they give positive results in a vast number of clinical conditions. Once the diagnosis of rheumatic fever is established, however, these procedures give the clinician invaluable information concerning the persistence of rheumatic disease. The most serious deficiency of the tests for activity, and it is one of considerble importance, is that they are unable to detect underlying disease activity when the symptoms and signs are suppressed by therapy. Thus when the overt manifestations of rheumatic fever are brought under control by either salicylate or hormonal therapy the sedimentation rate and C-reactive protein return to normal despite the fact that withdrawal of therapy will quickly show that the illness is merely suppressed and not cured. This poses an important problem since there is no way to determine how long therapy should be continued in the individual case except by trial and error. Some hope that a test may ultimately be available for detecting underlying disease activity in patients under suppressive therapy comes from the study of Kelley, Adams and Good on the serum mucoprotein in rheumatic fever.23 These workers found that the mucoprotein tended to remain at moderately elevated levels in contrast to the fall in the sedimentation rate during hormonal treatment, and they suggest that this may indicate persisting disease activity.

Although it is obvious that there is much room for improvement in the armamentarium of laboratory tests to be used in rheumatic fever, the physician receives invaluable assistance from the proper application of those that are now available. However, scientific precision in the diagnosis and management of rheumatic fever will not be possible until more specific and sensitive procedures are devised.

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Evolution of Murmurs in Early Rheumatic Heart Disease*

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of children with rheumatic fever develop cardiac murmurs during the stage of activity. On the other hand, interpretation of these murmurs varies with different observers because it is sometimes difficult to decide whether a certain murmur is due to ventricular dilation, acute inflammation of the valvular leaflets or valvular scarring. In the first instance, the murmur is caused by myocarditis; in the second, by active endocarditis; in the third, by healing or healed endocarditis.

An attempt to evaluate the significance of apical and pulmonic systolic murmurs was recently made by Luisada and Magri¹ through correlation of the clinical data with those supplied by phonocardiographic and electrokymographic tracings. A more prolonged electrocardiographic and phonocardiographic study was considered to be of interest.

MATERIAL AND METHOD

Forty-one pattents between the ages of two and fifteen were repeatedly studied at La Rabida Sanitarium or Mt. Sinai Hospital. When discharged from either hospital the patients were followed on Home Service at La Rabida or at the Pediatric Cardiology Clinic at Mt. Sinai Hospital, or came to La Rabida for a special check-up.

All patients were in their first rheumatic attack when first examined. The patients were followed for a period varying from several weeks to three years. Thirty-one patients recovered from the first attack during the period of observation and showed no further recurrence or relapse. In three patients the process had a chronic evolution with short periods of apparent recovery and subsequent relapses. In seven patients the

process was still in an acute phase at the end of the period of observation. All but five patients were treated with aspirin, hormones, or both.

The evolution of the rheumatic process was studied through physical, electrocardiographic, roentgenologic and laboratory findings. A phonocardiogram was taken whenever there was either a clinical change (acute phase, recovery, stabilization, rebound, exacerbation) or a change in the auscultatory data. A minimum of two phonocardiograms was taken in every case; in most cases, three phonocardiograms were taken (acute phase, recovery, stabilization); in some, from six to eight phonocardiograms were recorded.

The sound tracings were recorded by means of a Sanborn Twin-Beam with the patients in the supine position. The tracings were registered first with a stethoscopic, then with a logarithmic device, at a film speed of 75 mm./sec. When an aortic diastolic murmur was heard, a second logarithmic tracing with a membrane chest-piece was recorded at the base. The tracings were recorded over five different areas: apex, mid-precordium, pulmonic area, aortic area and tricuspid area (fourth intercostal space at the right of the sternum). When indicated, tracings of other areas were recorded.

The intensity of murmurs in the tracings was graded empirically as loud, medium, faint and very faint. They were timed as systolic and diastolic. The diastolic murmurs were distinguished by their pitch and by their timing (early diastolic, mid-diastolic, presystolic). When diastole was very short and a single murmur starting some time after the second sound occupied the rest of such phase, it was called mid-diastolic-presystolic. In general, a murmur was considered to have its point of origin where its intensity was greatest, and this seemed

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usually true for murmurs related to the mitral valve. Aortic diastolic murmurs were frequently recorded best at the left of the sternum.

Magnitude, configuration and type of vibrations allowed a division of the murmurs in five different types: in decrescendo, continuous

TABLE I
CONFIGURATION AND TYPE OF THE SYSTOLIC MURMUR OVER
THE DIFFERENT AREAS IN CASES OF GROUP I

Areas	Type of Murmur		t the inning	At the End		
		No.	Total	No.	Total	
Apex	Decrescendo	11		10		
	Continuous	1		2		
	Diamond-shaped			2		
	Musical	1				
	Minimal (nonde- script)	7	20	6	20	
Pulmonic	Diamond shaped	10	20	5	20	
ruimonic	Diamond-shaped Decrescendo	4		4		
	Minimal (nonde-	7		7		
	script)	5		6		
			19		15	
Aortic	Diamond-shaped	4		4		
	Decrescendo	5 2		4		
	Continuous Minimal (nonde-			2		
	script)	7		6		
			18		16	

systolic, diamond-shaped, musical and minimal (nondescript).

RESULTS

The evolution of murmurs in the tracings led to division of the patients into four groups.

Group I: Systolic Murmur Present at the First Observation. This group included twenty cases. The murmur was apical only in twenty, also pulmonic in nineteen, and also aortic in eighteen cases. A comparative study revealed that whenever there was a systolic murmur in decrescendo over the pulmonic or aortic area, it was transmitted from the apex.

The changes in magnitude and configuration of the vibrations of the systolic murmur during the period of observation are presented in Table 1 and Figures 1 to 3.

A triple rhythm was present in ten cases at the first observation. It was due to increased loudness of the third sound in five cases (Fig. 1); to in-

creased loudness of the fourth (atrial) sound in three; and to summation of both third and fourth sounds in two. It was present at the end of the observation in six cases because of a loud third sound. In one patient an opening snap of the mitral valve became apparent at the end of the

TABLE II
CONFIGURATION OF THE SYSTOLIC MURMUR OVER THE
DIFFERENT AREAS IN CASES OF GROUP II

Areas	Type of Murmur		t the inning	At the End		
		No.	Total	No.	Total	
Apex	Decrescendo	11		4		
	Continuous	1		4		
	Minimal (nonde-					
	script)	1		5		
			13		13	
Pulmonic		9		3 4		
	Continuous	1		3		
	Decrescendo	1		4		
	Minimal (nonde-					
	script)	1		1		
			12		11	
Aortic	Diamond-shaped	6		1		
	Continuous	1		2 5		
	Decrescendo	2		5		
	Minimal (nonde-			- 1		
	script)	1		2		
			10		10	

period while a mid-diastolic-presystolic rumble had appeared in another.

Three patients had roentgenologic evidence of a slight cardiac enlargement at the time of the first observation. The only case in which the x-ray showed enlargement at the time of the last observation was the patient in whom a mitral opening snap developed.

At the first observation the electrocardiogram showed a first degree a-v block in four cases and evidence of pericarditis in one. All tracings were normal at the last observation.

Group II: Diastolic Apical Murmur Plus Various Systolic Murmurs Present at the First Observation. This group included thirteen cases. The systolic murmur was only apical in thirteen cases, also pulmonic or aortic in eleven. Changes in loudness and configuration of the systolic murmur during the period of observation are presented in Table II.

The mid-diastolic or presystolic murmur was

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present at the first observation in all thirteen cases; at the last observation, only in five cases. (Fig. 4.) A triple rhythm was present at the first observation in eight cases; at the last, in ten cases. It was due to increased loudness of the third sound in the majority of cases.

cases at the beginning, in two at the end. A mid-diastolic or presystolic murmur was present at the beginning in two cases, at the end in one. The high pitched, early diastolic aortic murmur in decrescendo, which was present at the first observation in all four cases, increased in loud-

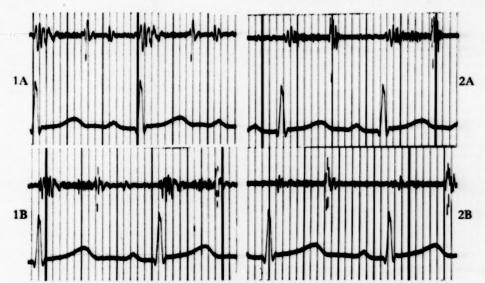


Fig. 1. Phonocardiograms at apex (stethoscopic). A, beginning of observation: faint systolic murmur, triple rhythm (loud third sound). B, end of observation: louder systolic murmur, less evident third sound.

Fig. 2. Phonocardiograms at apex (stethoscopic). A, beginning of observation: evident systolic murmur in decrescendo; poor intensity of first sound. B, end of observation: the murmur is less loud; the first sound is still of poor amplitude.

In six cases the x-ray showed cardiac enlargement at the beginning. At the end of the period the heart was of normal size in the patients whose apical diastolic murmur had disappeared. On the other hand, the heart was still enlarged in all but one case in patients still presenting the diastolic murmur.

The electrocardiogram showed first degree a-v block at the first observation in three cases. At the end the electrocardiogram was negative, except in one patient who showed an intermittent Wolff-Parkinson-White syndrome.

Group III: Apical Systolic and Aortic Diastolic Murmurs at the First Observation. This group included four cases. The systolic murmur was also present over the pulmonic and aortic areas. It increased at the apex during the course of the disease in one case; it decreased in another; and persisted unchanged in the other two. In all cases the pulmonic and aortic systolic murmurs remained unchanged during the entire observation. (Fig. 5.) The changes in configuration of the systolic murmurs are presented in Table III.

A triple rhythm was present in three of the four

TABLE III
CHANGES IN THE CONFIGURATION OF THE SYSTOLIC MURMUR
OVER THE DIFFERENT AREAS

Area	Type of Murmur		t the inning	At the End	
		No.	Total	No.	Total
Apex	Decrescendo Minimal (nonde-	2		2	
	script)	2		2	
Pulmonic	Diamond-shaped	4		4	4
Aortic	Diamond-shaped	3	•	3	*
	Minimal (nonde- script)	1		1	

ness in two and decreased or was unchanged at the last observation in the other two cases.

The x-ray showed cardiac enlargement in one case at the beginning, in two cases at the end. In

one of these the rheumatic process was still active at the end. A first degree a-v block was present in the electrocardiogram in two cases at the beginning and disappeared at the end. In the patient who was in an active stage and showed cardiac enlargement, a first degree a-v

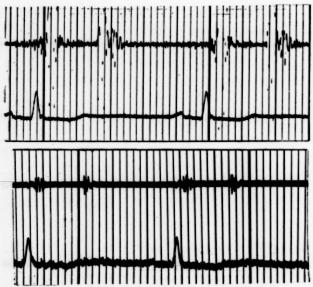


Fig. 3. Phonocardiograms over pulmonic area (stethoscopic) (same calibration). A, beginning of observation: large sounds; splitting of the second sound; faint systolic murmur. B, end of observation: no murmur, smaller sounds; no splitting.

block was present at the end. Three cases were treated with aspirin and one with cortisone.

Group IV: Minimal Systolic Murmur Either Diffuse or Localized. This group included four cases. The murmur was recorded either at the beginning or at the end of the observation period. The x-ray taken at the beginning revealed a prominent pulmonary artery in one of them. The electrocardiograms were negative both at the beginning and at the end of the period of observation.

DISCUSSION

Most of the patients of Group I presented a diffuse systolic murmur at the first observation. The apical murmur was in decrescendo, continuous or musical (regular vibrations) in fourteen cases; it was minimal and nondescript in the others. These graphic characteristics indicated that it was a mitral regurgitant murmur in all cases. The pulmonic and aortic murmurs, on the other hand, were diamond-shaped only in some of the cases, of various configuration in the others. As the basal systolic murmur caused by stenosis is diamond-shaped, 2-4 it is apparent that

about one-third of the basal murmurs were transmitted from the apex, a fact which is more common in children than in adults.

At the end of the period of observation the apical systolic murmur had decreased or disappeared in one-half of the cases (Fig. 2) and had increased in the other half. (Fig. 1.) It is logical to conclude that the apical systolic murmur initially observed was due to dilatation of the mitral ring or stretching of the papillary muscles caused by carditis (relative mitral insufficiency), while that observed after disappearance of rheumatic activity was due to an already established mitral lesion (organic insufficiency).

The pulmonic systolic murmur, not transmitted from the apex, was present in about one-half of the cases at the beginning, in one-fourth of the cases at the end. This confirms the previous impression of Luisada and Magri¹ that a pulmonic systolic murmur of local origin is more common in the early than in the later stages of rheumatic activity. Two explanations can be advocated, dynamic dilation of the pulmonary artery (fever, increased pulmonic pressure or flow) or organic dilatation of this vessel (rheumatic arteritis).

The aortic systolic murmur, not transmitted from the apex, was present in about one-fifth of the cases both at the beginning and at the end. Therefore, it is logical to explain this murmur as evidence of an organic stenosis of the aortic valve which started early in the course of the disease.

A triple rhythm (gallop rhythm) was present in about one-half of the cases at the beginning; in about one-third at the end. The connection between tachycardia, ventricular strain and triple rhythm is too well known^{3,4} to need discussion. It should be emphasized that this triple rhythm, previously noted by others,^{5,6} is the result of carditis and that it is frequently mistaken, upon auscultation, for a mid-diastolic murmur.

The patients of Group II, in addition to systolic murmurs similar to those of Group I, also had an apical diastolic or presystolic rumble. While at the first observation this murmur was present in all thirteen cases, at the last observation it was present only in five cases, a decrease of nearly two-thirds. All these were severe cases; most of them were treated with ACTH or cortisone; several presented evidence of congestive failure. The most logical explanation is that of a low pitched murmur caused by "relative mitral and tricuspid stenosis," i.e., ventricular dilation. This explanation was first advanced

following auscultatory studies^{7,8} and was further demonstrated on the basis of graphic evidence. 9,10 In those instances in which no cardiac enlargement was demonstrated, edema of the mitral leaflets may be suggested as an alternative explanation.

gross evaluation of the intensity of a murmur through electric and clinical calibration. 11 Although this evaluation is not altogether exact, it is far more accurate than clinical evaluation which may mistake changes in the pitch of the murmur for changes of intensity. 12 (3) It gives

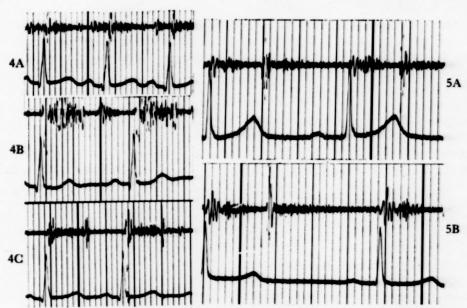


Fig. 4. Phonocardiograms at apex (stethoscopic). A, beginning of observation: presystolic murmur and systolic murmur in decrescendo. B, two months later: greater intensity of systolic murmur; mid-diastolic murmur with large vibrations. C, end of observation: visible, long, systolic murmur; disappearance of the diastolic

Fig. 5. Phonocardiograms over the pulmonic areas (logarithmic). A, beginning of observation: systolic murmur, early diastolic murmur in decrescendo (of aortic origin). B, end of observation: both the systolic and the diastolic murmur have a greater intensity.

The patients of Group III had both apical and basal systolic murmurs and an aortic diastolic murmur. The latter persisted in two of the four cases, was unchanged in one and in one case had decreased at the end of the period of observation. This murmur was undoubtedly caused by aortic insufficiency. On the other hand, it is well known that an aortic diastolic murmur, present during the active rheumatic stage, may disappear later. Any explanation of this phenomenon would be purely speculative.

The patients of Group IV had a minimal systolic murmur and it was impossible to localize the valve responsible for the murmur.

COMMENTS

In comparison with auscultation, phonocardiography presents the following advantages: (1) It gives objective proof of the existence of murmurs, extra-sounds, or both. (2) It allows a

a picture of the "shape" and "aspect" of the murmur (crescendo, decrescendo, continuous, diamond-shaped, musical) thus pointing out the most likely valvular source of origin. (4) By confirming the complete disappearance of a murmur, it reveals that the latter was caused by a muscular (myocarditis) and not a valvular (endocarditis) lesion.

The present study revealed that the mitral systolic murmur decreased or disappeared in about one-half of the cases (Groups I and II) while it was unchanged or was louder in the other half. This was considered evidence that the murmur was either completely or largely "myocardial" in the first half of the cases. However, moderate involvement of the mitral leaflets may not be revealed by murmurs13 and it is therefore possible that some of these patients actually had a healed valvular lesion at the end of the period of observation.

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In the patients of Group II the diagnosis of mitral stenosis caused by previous attacks was considered established until disproved by the clinical course. The phonocardiogram revealed certain typical features of the murmur which indicated it to be due to a "relative stenosis." In most cases these features were: large amplitude of the vibrations, wide area of recording, and beginning of the murmur with a loud third sound. In two-thirds of the cases phonocardiograms revealed subsequent complete disappearance of the murmur, thus confirming its "functional" nature.

The four patients of Group III also had an aortic diastolic murmur which decreased at the end of the period of observation only in one. This confirms the clinical impression that aortic diastolic murmurs are seldom transient, although the possibility of disappearance of such murmurs should be admitted.

SUMMARY

A clinical and phonocardiographic study was made in forty-three patients at the first attack of rheumatic fever and was repeated until either recovery or a definite chronic course was evident.

The patients were divided into four groups: (1) Those who had only systolic murmurs at the first observation. This group included twenty cases; murmurs were present at the apex, pulmonic and aortic areas for the most part. The murmurs decreased or disappeared in about onehalf of the cases; they increased in the other half. About one-third of the basal systolic murmurs were proved to be transmitted, while two-thirds were of aortic or pulmonic origin. A significant pulmonic systolic murmur was present in one-half of the cases at the beginning, in about one-fourth at the end. A significant aortic systolic murmur was present in one-fifth of the cases both at the beginning and at the end. (2) Those who had both a systolic murmur and a diastolic rumble at the apex at the first observation. These were all severe cases. At the end of the period of observation nearly twothirds of the patients showed no further evidence of the diastolic rumble. (3) Those who had an apical systolic and an aortic diastolic murmur

at the first observation. The aortic diastolic murmur subsequently decreased in one case; it persisted or increased in the others. (4) Those with minimal, diffuse murmurs.

Among other points discussed are: (1) the advantage of using phonocardiographic documentation for the study of rheumatic patients, (2) the frequency of triple rhythm, and the pathogenetic mechanisms involved; (3) the mechanism of production of the various murmurs, and the possibility of distinguishing a diastolic rumble due to "relative" stenosis from one caused by organic mitral stenosis.

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Recent Advances in the Diagnosis of Rheumatic Heart Disease*

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IAGNOSIS in rheumatic heart disease includes recognition of the etiology of the process and evaluation of myocardial, endocardial and pericardial lesions. It also includes evaluation of possible lingering activity of the rheumatic process.

The diagnostic problem can be summarized by the following questions: (1) Is the patient a rheumatic? If so, when did the first episode of rheumatic fever take place; were there subsequent acute episodes? (2) Has there been any myocardial damage? Is there any evidence of active rheumatic myocarditis? (3) Has there been any pericardial lesion? If so, what was its importance? (4) Is there any valvular damage? Which are the damaged valves? How can we evaluate the severity of each lesion?

These questions will be discussed in the same order, and emphasis will be placed on recently developed diagnostic procedures which may help in finding an answer.

Is the patient a rheumatic? This first question can often be answered by the history and physical examination of the patient. A clear-cut history of rheumatic fever many years before the examination plus the physical finding of one or more murmurs represent positive and definite evidence. However, the following points should be kept in mind: (1) The patient may not be aware of ever having had rheumatic fever (actually, a large percentage of the cases of mitral stenosis have a negative history). (2) An episode which took place during infancy and was called rheumatic fever may actually have been an arthritis of different nature or an infection. (3) Even though rheumatic fever is most common between six and twenty years of age, it may occur at any age. Cases in young children are being reported in greater number,² as are cases in the aged.3 As evaluation of the murmurs is sometimes difficult, there are cases in which an

etiologic diagnosis should be deferred until a complete study of the patient has been made.

Has there been any myocardial damage? Is there evidence of active rheumatic carditis? When the patient has a positive history of rheumatic fever and was repeatedly observed, the old records—in particular the electrocardiograms—may answer this question. Prolongation of the P-R or Q-T interval, bundle branch or intraventricular block, polyfocal extrasystoles, episodes of tachycardia from an ectopic focus, atrial flutter or fibrillation, occurrence of A-V or S-A blocks, all are evidence of severe carditis. Myocardial damage may be revealed by minor changes of the electrocardiogram, in particular by a P-R interval of excessive duration or by slurring of QRS.

Evidence of rheumatic carditis can be deduced in four ways: (1) By observation of recent electrocardiographic changes (long P-R, long Q-T, or indications of increased excitability or block); (2) by laboratory tests (leukocytosis, anemia, C-reactive protein, high sedimentation rate); (3) by the appearance or intensification of murmurs confirmed by phonocardiography or by roentgenologic evidence of gradual enlargement of the heart; (4) by the occurrence of congestive failure, especially if in a young individual or if not explained by previous history of unusual strain, infection or coronary occlusion.

If it is concluded that the patient is a rheumatic subject, had myocardial damage and that there is a process of active rheumatic carditis, treatment should be chiefly directed against the inflammatory process (cortisone, salicylates). Oxygen, digitalis, mercurials and diamox® should be used only as adjuvants and only if there is heart failure.

Has there been any pericardial lesion? If so, what is its importance? History of a friction rub at any age or recollection of precordial pain (in the young)

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coinciding with an acute episode of rheumatic fever can be taken as evidence that the pericardium was involved during the acute stage of the disease. Electrocardiographic patterns indicating pericarditis are also evidence of this involvement. However, a careful differential diagnosis between the patterns of myocardial and pericardial damage is sometimes necessary.

In general, rheumatic pericarditis heals without extensive adhesions but may leave bands of fibrotic tissue which do not cause constriction. If there is a diffuse adhesive pericarditis, this usually develops at a stage in which the heart is large, and fails to reduce the cardiac volume by constriction. However, cases of rheumatic constrictive pericarditis have been reported.

String-like adhesions may aggravate the clinical picture if located around the large veins and diffuse pleuropericardial sinechia may also contribute to dyspnea or hepatic engorgement. Crunching sounds or snaps may be caused by pericardial adhesions as early as a few months after the acute episode. This possibility should be known in order to differentiate them from diastolic gallop sounds or murmurs.

Is there any valvular damage? This question, which until a decade ago was answered in the affirmative if murmurs were present, needs further qualification and discussion.

1. Children and adolescents may present systolic murmurs which have been the object of several investigations. While one school of thought considers that all "musical" or "seagull cry" murmurs are "innocent" and do not indicate a valvular lesion, 4-6 the author and his co-workers^{7,8} have emphasized the frequency of "musical" pulmonic murmurs in rheumatic children and noticed their disappearance (both by auscultation and phonocardiography) during the evolution of the disease. Pending the results of a current clinical, graphic and roentgenologic study in children of school age,9 it would be advisable to consider that systolic murmurs may be caused by obsolescent rheumatic carditis, increased pulmonic flow (congenital heart disease) or anemia. In all three instances, even though a non-valvular mechanism is the cause of the murmur, this is certainly not "innocent." The author therefore suggested abandonment of the term "functional murmur" as misleading and to adopt instead that of "murmur of unknown origin."10

On the other hand, when a systolic apical murmur has been recognized as caused by rheumatic carditis, several pathogenetic mechanisms may be involved, as proven by an electro-kymographic study.⁷ The problem then to be solved is whether the murmur indicates muscular or valvular damage, and it is often difficult to evaluate the severity of damage which might be present at a later date.

2. An apical diastolic murmur always has a serious meaning. However, it should not be too lightly admitted as evidence of mitral stenosis. An apical mid-diastolic murmur may be simulated by diastolic extra-sounds (usually a loud third sound)5,11,12 and a presystolic murmur may be simulated by a crescendo-type first sound.12-15 These auscultatory illusions are easily recognized by means of phonocardiography. 13,16 Mid-diastolic or presystolic murmurs may be caused by acute rheumatic carditis and are probably due to "relative" mitral or tricuspid stenosis (dilatation of either ventricle).5 Phonocardiography frequently permits recognition of the functional nature of these murmurs, and exclusion of organic mitral stenosis. 17 On the other hand, mitral stenosis should not be excluded simply because of the early age of the patients.

When acute rheumatic carditis has been excluded as a cause of murmurs, and established valvular lesions are considered present, the next problem is to localize the site of valvular damage. This problem is far more complex than the others. It has become even more important in the last few years because an accurate structural diagnosis is needed before considering surgical repair.

MITRAL VALVE LESIONS

Mitral valvular lesions without damage to other valves are common in rheumatic heart disease. It is likely that during life mitral stenosis is always accompanied by some degree of insufficiency even though this may be minimal or hemodynamically insignificant. Mitral insufficiency, however, may exist without mitral stenosis. Therefore, differential diagnosis should be made between (1) mitral insufficiency, (2) mitral insufficiency and stenosis and (3) mitral stenosis (with insignificant insufficiency). The large number of technical methods which were applied to the solution of these problems requires a systematic listing. A more detailed description can be found in a comprehensive work of the author.16

Physical Examination. Low Frequency Tracings: Physical examination (inspection, palpation) supplies data which may be confirmed by low frequency tracings of the precordium. 12,16-18 Severe mitral stenosis with little insufficiency is revealed by a heaving pulsation of the central area of the precordium and of the epigastrium. 19 The low frequency tracing shows a positive pulsation of the left sternal region¹⁹ and of the epigastrium¹⁸ during systole, while the apex has no pulsation or shows a systolic depression.18 These findings are due to right ventricular hypertrophy, with frequent clockwise rotation of the heart around its longitudinal axis. Severe mitral insufficiency is revealed by a heaving apical thrust. The latter is displaced downward and to the left on account of left ventricular hypertrophy. The low frequency tracing shows a high positive wave at the apex and a negative pulsation at the epigastrium.18 The association of severe mitral insufficiency and stenosis gives less distinctive signs.

Auscultation. Phonocardiography: Auscultation may supply useful diagnostic signs. However, several causes of error inherent in the mechanism of audition indicate the need for graphic tracings. The most reliable, in the author's view, is a "stethoscopic" tracing which gives a more accurate reproduction of those vibrations (between 10 and 50 per second) which are poorly heard.²⁰

Severe mitral stenosis is revealed by well known auscultatory characteristics during diastole (opening snap; mid-diastolic murmur; presystolic murmur; snapping, loud and delayed first sound at apex; split second pulmonic sound). However, several causes of error are possible: Mitral insufficiency may be the cause of either a triple rhythm (gallop) or a "relative mitral stenosis" because of increased left atrial pressure and left ventricular enlargement. Phonocardiographic tracings may clarify the diagnosis in most cases. 13,16 The murmur of "relative stenosis" usually has a large amplitude, starts late in diastole with a loud third sound and can be recorded over a large area of the precordium. Moreover, the first sound is delayed over QRS of the electrocardiogram in organic mitral stenosis21,22,30 whereas it bears a normal relationship in "relative" mitral stenosis. 16 The interval between the Q wave of the electrocardiogram and the largest vibration of the first sound (Q-1 interval) has a typical variability in cases of mitral stenosis with atrial fibrillation,

as shown by the author²⁷ and confirmed by others.^{21,22,30,38} This variability is absent unless there is narrowing of the mitral valve. The opening snap of the mitral valve also has a certain importance. It has been stated that an opening snap excludes severe mitral insuffi-

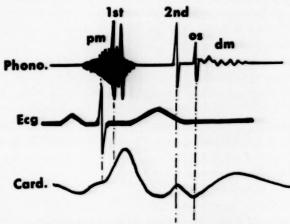


Fig. 1. Scheme of the sound tracing (Phono), apex cardiogram (Card), and electrocardiogram (Ecg) in severe mitral stenosis with sinus rhythm. The opening snap (os) coincides with the lowest point of the cardiogram; delay of first sound.

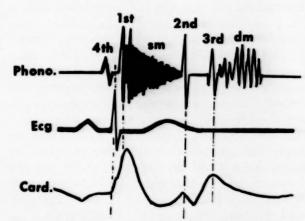


Fig. 2. Scheme of the sound tracing (Phono), apex cardiogram (Card), and electrocardiogram in a case of mitral insufficiency with "relative" or "functional" mitral stenosis. The third sound coincides with the wave of rapid filling of the cardiogram; no delay of first sound. Compare this with Figure 1.

ciency,²³ and indicates that the leaflets are still mobile.²⁴ However, absence of the opening snap in a case with a typical diastolic rumble at the apex may be due to extensive calcification of the leaflets.²⁵ (Figs. 1 and 2.)

If it is true that the pressure gradient across the mitral orifice is the main factor which determines the duration of the Q-1 and 2-OS intervals, 30 the severity of mitral stenosis might be evaluated

by plotting the R-R interval against the former two intervals. It has been stated that if Q-1 minus 2-OS is over -1, mitral stenosis is severe; whereas if it is below -1.5 the orifice is larger than 1 by 1 cm. and valvulotomy should not be considered. This statement needs confirmation.

Absence of a diastolic rumble in cases of mitral stenosis is possible.²⁶ In general, this absence is temporary and takes place in patients with atrial fibrillation and either a very rapid or a very slow ventricular rate. Usually, moderate exertion brings out the typical murmur. In cases of "silent" mitral stenosis the phonocardiogram usually reveals one or more of the following findings: (1) an opening snap; (2) a low-pitched (inaudible) diastolic rumble; (3) a delayed first sound; (4) a variable interval between QRS and first sound (atrial fibrillation).

Severe mitral insufficiency is revealed by a loud (grade 3 or 4) apical systolic murmur with typical transmission toward the left axilla and the back, and poor transmission toward the right side of the precordium. This murmur is usually soft and not accompanied by a thrill. Exceptions are possible and rare cases with a harsh systolic murmur and a thrill have been observed by the author. The phonocardiogram reveals a systolic apical and mid-precordial murmur which, in the experience of the author,16 is either in decrescendo or, more seldom, allsystolic. A systolic murmur in crescendo is exceptional, although considered the rule by others.28 A differentiation from certain types of congenital heart diseases is usually possible because the latter have a more centrally located systolic murmur with lesser transmission toward the axilla and greater spread toward the right side and the base. The murmur of congenital heart disorders is made up of coarser vibrations and is either all-systolic (ventricular defects) or diamond-shaped (atrial defects, pulmonic stenosis). Mitral insufficiency unaccompanied by stenosis always is associated with a systolic murmur the intensity of which, however, is not proportional to the severity of the defect.

Mitral stenosis plus insufficiency frequently is associated with a systolic murmur in addition to the diastolic rumble. However, the systolic murmur may be absent even when mitral insufficiency is proven by electrokymography (v. seq.) or surgery.²⁹ The first sound of patients with insufficiency and stenosis maintains a constant relationship to the QRS of the ECG whenever

there is atrial fibrillation, in contrast with cases with pure stenosis.³⁰

Electrocardiography-Vectorcardiography. The electrocardiogram of mitral valve defects is modified by several factors, chiefly dilatation or hypertrophy of either ventricle or of the left atrium, and fibrosis of the conducting system or of the atrial or ventricular myocardium. The electrocardiogram of mitral stenosis has been considered typical for a long time. The following changes are undoubtedly common: (1) P wave changes consisting of high and notched P1 and diphasic P3 and PV1. When P is diphasic, a low initial positive phase followed by a deep, broad, negative phase in the right precordial leads, would indicate left atrial enlargement. On the other hand, a high, initial, positive phase and a narrow, small negative phase would indicate a severe increase of right heart pressures (right atrial pattern). Direct, unipolar leads of the two atria have revealed high P wave voltage and increased delay of the left atrial complex over the right (0.05 instead of 0.03); this delay is greater when the left atrial myocardium is damaged.31 (2) Tendency toward right axis deviation and evidence of right ventricular hypertrophy. The latter is grossly proportional to right ventricular pressure.32 (3) Occurrence of atrial premature beats or atrial fibrillation; (4) possible occurrence of right bundle branch block or intraventricular block.

The vectorcardiogram affords more distinct differentiation of the various causes (rotation, hypertrophy, block) of the ventricular pattern of mitral stenosis.³³

Mitral insufficiency: The electrocardiogram in mitral insufficiency shows left axis deviation in about one-third of the cases, 28 never right axis deviation. Electrical evidence of left ventricular hypertrophy is present in one-half of the cases. 28 The P waves usually have a normal voltage and there is no abnormal pattern. Ventricular extrasystoles may be present. 28

Cases with both stenosis and insufficiency present the picture of the predominant defect. Thus left ventricular hypertrophy may confirm the presence of associated insufficiency in cases with auscultatory findings typical of stenosis (an associated aortic lesion should be excluded).

Ballistocardiography. Many patients with rheumatic heart disease and apical murmurs have normal ballistocardiographic patterns. Others, though free of symptoms, show an increase of respiratory variations and large H, L or N

waves.³⁴ No typical pattern seems to exist in "pure" mitral stenosis except for decreased amplitude of the HI waves, without change of the JK segment.³⁵ A significant change has been repeatedly described in the systolic complex.^{36–38} It consists of the appearance of a new, large wave in early systole prior to J, simulating alterations of the G and I waves. This new headward wave has been interpreted as caused by a systolic, regurgitant jet into the left atrium and would therefore indicate the presence of mitral regurgitation.

Pressure Tracings. Interpretation of pressure tracings from the left atrium requires a clear understanding of the normal pressure curves of the atria and ventricles and of their possible changes in mitral valve diseases. The normal atrial tracing consists of a small presystolic, positive wave (a wave due to atrial contraction); a deep systolic collapse (traction by the ventricle over the a-v floor); and a gradual, late systolic rise culminating in a peak which coincides with the early diastolic opening of the mitral valve (v wave due to gradual filling of the atrium). Mitral stenosis increases the height of the presystolic wave (left atrial hypertrophy) and that of the early diastolic wave (higher filling pressure). Mitral insufficiency gives an entirely different pattern consisting of a rectangular plateau. This is due to the fact that the left ventricle and the left atrium are in communication during ventricular systole, and the plateau pattern is typical of tracings from the ventricle because a sustained effort of the ventricular myocardium keeps the pressure at an even level during most of systole.* For this reason, a plateau pattern in tracings of the left atrium (intracardiac pressure, esophageal pressure, electrokymogram) is the direct result of insufficiency. A rounded wave in systole may also be the result of regurgitation but is less typical unless the left ventricle is failing. (Figs. 3 and 4.)

Pressure tracings of the left atrium have been recorded by means of a needle introduced through the appendage during cardiac surgery, ³⁹ through the left main bronchus, ^{40,41a} from the suprasternal fossa ⁴³ or from the right side. ^{41a} These tracings reveal that in "pure" mitral stenosis a steep, oblique line forms the ascending

* This pattern may be distorted by inadequate transmission (catheters) or inaccurate recording apparatus. It can be found in experimental tracings from the left ventricle and in the best tracings from the right ventricle of man.

branch of the "v" wave, while the presence of mitral regurgitation is revealed by a systolic plateau.

Pressure tracings of the left ventricle have also been recorded by introducing a catheter through a needle previously placed into the left atrium. 416

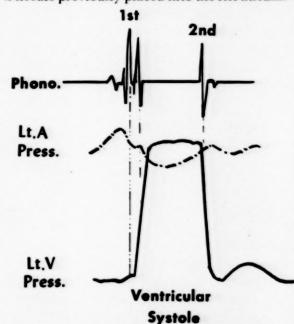


Fig. 3. Superimposed tracings of left atrial and ventricular pressures in man. The phonocardiogram (Phono) gives the timing of the waves.

Comparison of left atrial with left ventricular tracings may be helpful in evaluating the degree of mitral insufficiency and stenosis.

Esophagocardiograms. Typical patterns have been described in mitral insufficiency. 45,46 More recently, different types of tracings have been studied. The configuration of the eosphageal pulse was studied by means of tambours, 45-47 through pressure tracings from the esophagus, 48 or both. 49,50 Interpretation of the tracings is not uniform. Some believe that a typical plateau wave* in systole indicates mitral insufficiency while others consider more typical a rounded wave⁴⁷ or a late systolic peak superimposed upon a plateau. 48 The disagreements are mostly caused by the fact that cases of "clinically" pure mitral stenosis may present a plateau wave, which has led some to believe that the esophagocardiogram supplies data of diagnostic value in mitral insufficiency but not in mitral stenosis (with or without insufficiency).47

A conclusion which can be accepted⁴⁹ is that:
(1) the esophagocardiogram shows a typical

^{*} The diagnostic significance of a plateau-wave has been already discussed (see pressure tracings).

pattern in mitral insufficiency; (2) this pattern is frequently found in cases of mitral stenosis even though sometimes no regurgitant jet is felt by the surgeon;* and (3) that efforts to quantitate mitral regurgitation by the esophagocardiogram are somewhat disappointing. Still,

(2) if the atrial border is not clearly visualized because of extreme enlargement or superimposition of extracardiac shadows. There is general agreement that the greatest enlargement of the atrium is usually found in mitral regurgitation.

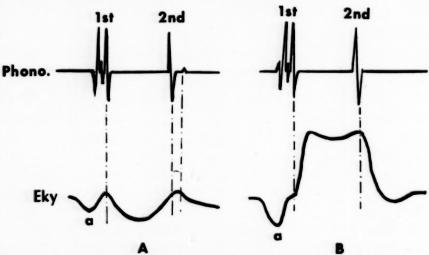


Fig. 4. Left atrial tracings (electrokymogram or esophageal tracing). A, normal tracing; B, severe mitral regurgitation. This tracing resembles one of ventricular pressure with addition of one of atrial pressure (compare with Figure 3). The resultant is a characteristic plateau.

the most critical investigators consider the esophagocardiogram superior to fluoroscopy in evaluation of the systolic expansion of the left atrium caused by regurgitation.

Roentgenology. Roentgenology permits recognition of two different pictures: that of mitral insufficiency with enlarged left atrium and left ventricle, and that of mitral stenosis with enlarged left atrium and right ventricle. While these abnormalities are clearly recognizable in "pure" disturbances of function of the mitral valve, the degree of associated insufficiency cannot be accurately estimated in cases of mitral stenosis.

Enlargement of the left atrium cannot be demonstrated in a certain number of cases of mitral stenosis by either fluoroscopy or esophagogram, even though it is present.⁵¹ On the other hand, such enlargement may be absent.^{52,53} The contrast between large hilar vessels and clear lung fields has recently been interpreted as indicating severe pulmonary vasoconstriction with high pulmonary arterial pressure.⁵⁴

Systolic expansion of the left atrium was recognized on fluoroscopy a long time ago and accepted as evidence of mitral regurgitation. However, this observation is not possible (1) if there is severe tachycardia or arrhythmia or

Roentgenkymography. Thorough observations have been made both in mitral insufficiency and stenosis. 55 A pattern of expansion was noted over the left atrial border in many cases of mitral valve lesions with or without a systolic murmur. 55 However, this pattern was most typical and constant in severe mitral regurgitation. The technical limitations of the method do not allow good visualization of the waves in all cases. The possibility of roentgenkmyographic differentiation between mitral stenosis and mitral stenosis with insufficiency was recently claimed. 56

Electrokymography. This new method of investigation was perfected between 1945 and 1948. 57-59 It suffers from some of the anatomic limitations of roentgenkymography but its technical limitations are far less. In particular, the possibility of amplifying at will the amplitude of the waves without decreasing the accuracy of the tracing is a great advantage over roentgenkymography.

A first study of the border tracings of the left atrium in mitral valve lesions was made in 1948.⁶⁰ A typical pattern consisting of a systolic plateau was described and attributed to *mitral regurgitation*. Changes of the atrial, presystolic wave were also described in *mitral stenosis*. As the plateau pattern was present even in cases with-

^{*} This diagnostic sign will be evaluated subsequently.

out a systolic murmur, it was concluded that the auscultatory and phonocardiographic findings were less revealing than those of electrokymography. This conclusion was similar to that previously reached by others working with roentgenkymography⁵⁵ and was subsequently

3. The tracings should be recorded at a high film speed (75 or 100 mm./sec.) in order to spread the waves and to permit accurate timing (best timing by comparison with a sound tracing). Normal persons occasionally present one or two tracings with a positive wave in systole

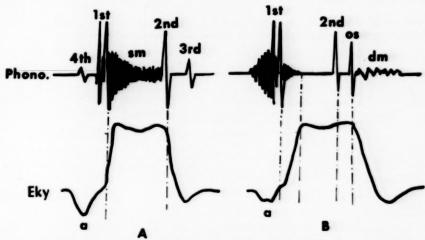


Fig. 5. Relationship of the electrokymographic plateau pattern to ventricular systole. A, predominant insufficiency = early plateau; B, predominant stenosis = late plateau.

confirmed by several authors. 61-74 In general, these authors agreed that an atrial tracing with a plateau pattern was indicative of rheumatic heart disease with mitral valve lesion but was so common in such patients that it could not be used for selection of candidates for surgery (this point will be discussed subsequently). A few others considered the method with skepticism because they found a similar plateau pattern in normal subjects. 49,75 This statement, which does not coincide with the findings of the author, was refuted by a subsequent study⁷⁶ in which the technical causes of error were explained in detail.

Having systematically studied patients with mitral valve lesions for the last eight years, we can add some personal data to those previously published:

1. The left atrium should be studied in several projections: (a) left oblique (two tracings); (b) right oblique (two tracings); (c) right lateral (two tracings). To these should be added a densogram in the right lateral projection and, if possible, a tracing of the left atrial appendage in the postero-anterior position. Thus eight tracings should be recorded.

2. Calibration should be made in every tracing so that relative evaluation of the magnitude of the waves can be accomplished.

due to superimposition of pulsating vessels. However, the rise of the wave is gradual and there is a dicrotic wave in diastole. Those tracings can be easily recognized. The typical pattern of regurgitation is that of a plateau (sometimes with superimposition of a slight depression on top due to lowering of the a-v floor in systole). Patients with mitral stenosis and high pressure in the left atrium have an earlier filling which may be revealed by a rise of the curve during the latter part of systole. Whenever the tracings show in several projections (a) a rise during early systole, (b) a flat top and (c) a drop in early diastole without rebound, the presence of mitral regurgitation should be admitted. A subsequent step consists of evaluating the severity of this disturbance. A first possibility is supplied by calibration which permits one to quantitate, even though approximately, the amplitude of the waves. One calibrating device has been described,95 another is presently in use in our laboratory. A second possibility is based on the study of the time of appearance of the plateau, as proven by a current investigation in our laboratory91 based on the study of eightytwo cases of mitral valve lesion. Of these, sixteen were operated on and a comparison could be made between preoperative EKY, postoperative EKY, and findings of the surgeon. In two other

cases death occurred and the autopsy findings were compared with the EKY data. By analogy with observations of others in venous types of tracings, ⁹⁶ it was considered that the time of onset and termination of the plateau could be used for diagnosis, a late appearance being indicative of

However, it should be explained by increased motion of the strongly contracting appendage and not by increased magnitude of emptying.

This survey of the electrokymographic data should be concluded with a note concerning the diagnosis of mitral insufficiency made during

TABLE I
COMPARISON OF ELECTROKYMOGRAPHIC, SURGICAL AND AUTOPSY FINDINGS

	No. of Cases	Diagnosis at Surgery			Diagnosis at Autopsy		
Preoperative EKY Pattern		Mitral Stenosis	Mitral Insufficiency	Mitral Stenosis plus Insufficiency	Mitral Stenosis plus Insufficiency	Postoperative EKY Pattern, No. of Cases	
Late plateau (predominant stenosis)	13	11		2		5 (of 5 observed) showed earlier plateau	
Early plateau (predominant insufficiency)	5	1	2		2	2 (of 2 observed) showed earlier plateau	

narrowing of the valve. It was observed that cases in which all clinical data were in favor of a severe mitral stenosis had a delay in the beginning of the plateau (more than 0.10 sec. after the first loud vibration of the first sound) and a protracted end of the plateau (end after the opening snap of the mitral valve). On the other hand, cases in which all clinical data were in favor of an isolated or predominant insufficiency had an early onset (less than 0.10 after the first sound) and an early end of the plateau (simultaneous with the end of the second sound). (Fig. 5.) Of the thirteen cases with late plateau, predominant stenosis was confirmed in nine cases by surgery; of five cases with early plateau, equivalent or predominant insufficiency was confirmed in two cases by surgery and in two others by autopsy. Thus the electrokymographic diagnosis of predominant stenosis of the mitral valve, based on the timing of the plateau pattern, was in agreement with surgical findings in 84 per cent of the cases while the electrokymographic diagnosis of predominant insufficiency was confirmed by either surgery or autopsy in 80 per cent of the cases. Surgery modified the onset and ending of the plateau in all cases which came to observation, the pattern revealing a greater insufficiency and a lesser degree of stenosis. (Table 1.)

It has been stated that the presystolic atrial wave in mitral stenosis is much larger over the left appendage.⁷² We can confirm this fact.

surgery. Surgical evaluation is made in patients who are under deep anesthesia, have an open chest, and are on their right side.* Under such conditions the cardiac output is lower, the cardiac rate higher and the energy of left ventricular contraction decreased. Therefore, surgery may fail to disclose moderate insufficiency while electrokymography may overemphasize it through its tremendous power of magnification. Calibration and analysis of the tracing ought to remedy this practical shortcoming of the graphic method.

Catheterization of the Right Heart. This is discussed in detail elsewhere in this symposium.

AORTIC VALVE LESIONS

Aortic valvular lesions without damage to other valves are usually recognized without difficulty. The diagnostic problem is more difficult in certain cases.

There may be doubt as to whether the patient has syphilitic or rheumatic heart disease. In the first instance there is aortic regurgitation, no aortic stenosis, and usually no lesion of the mitral orifice. Recognition of aortic stenosis (carotid tracing, electrokymogram of left ventricle and of aortic arch^{15,83}), mitral insufficiency (phonocardiogram at apex, electrokymogram of left atrium^{60,76}) or mitral stenosis (electro-

^{*} Recent studies show a pattern of left atrial pressure differing according to the position of the patient. 41a

cardiogram reveals right axis shift or right ventricular hypertrophy; phonocardiogram revealing the apical murmur) swings the balance in favor of a rheumatic etiology. Differentiation between an apical diastolic rumble of "functional" nature (Austin Flint murmur) and the murmur of mitral stenosis can frequently be made by means of the phonocardiogram.¹⁶

The patient has a rheumatic mitral lesion and the problem is whether or not there also is an aortic lesion. In the absence of mitral regurgitation, electrocardiographic (left axis shift, left ventricular hypertrophy) and roentgenologic (enlargement of left ventricle) data; a large pulse pressure; and the data supplied by auscultation and phonocardiography (diamond-shaped systolic murmur or early diastolic murmur over the aortic area^{15,82}) are usually sufficient for the diagnosis. The ballistocardiogram may show typical findings in aortic insufficiency³⁶ and stenosis.^{93,94}

The following data should be considered significant in indicating aortic stenosis. The carotid tracing, the aortic electrokymogram, and the intrabrachial pressure tracing reveal a slow ascending phase, often with an early depression (anacrotic pulse)15 and the vibrations of a systolic thrill (carotid shudder⁸⁴). The ballistocardiogram may present small or absent K waves93 or a typical angulation of the J-K segment.94 If necessary, direct measurement of left ventricular pressure 416 may be resorted to; systolic pressure higher within the left ventricle than in the brachial artery is evidence of valvular obstruction. Bradycardia and the presence of an auscultatory gap (blood pressure readings) give confirmation.

The differential diagnosis between aortic stenosis of rheumatic etiology and aortic stenosis due to atherosclerosis may be extremely difficult. The presence of an associated mitral stenosis would be in favor of a rheumatic lesion. The differential diagnosis between rheumatic aortic stenosis and a systolic aortic murmur due to atherosclerosis or aortitis without obstruction is based on definite positive (carotid shudder, anacrotic pulse) and negative (weak or absent second aortic sound) data which can be found only in cases with aortic stenosis obstructing the flow.

Congenital aortic stenosis is frequently subaortic, in which case there is a typical murmur with maximum intensity at the third left interspace but radiating toward the neck. If valvular, the characteristics are similar to those of rheumatic aortic stenosis. Therefore, the clinical picture cannot indicate the etiology unless associated defects or lesions are present or there is a positive history.

TRICUSPID VALVE LESIONS

Tricuspid lesions are usually associated with mitral lesions; therefore, the diagnostic problem consists of ascertaining whether or not a patient with rheumatic mitral disease also has a tricuspid defect. A typical clinical picture (no orthopnea, limited pulmonary congestion, hepatomegaly, ascites, peripheral edema, subicterus) was described long ago.

Tricuspid insufficiency is easy to diagnose on the basis of the marked systolic pulsation of the jugular veins and the liver. The systolic pulsations have a plateau-like pattern15,85 due to transmission of a ventricular pressure pattern to the veno-atrial system. Recording of the jugular or hepatic tracings is easy by using a piezoelectric system. 15 Phonocardiography is of help in confirming the existence of a systolic murmur over the xiphoid process or at the right of the sternum, a murmur which sharply increases in inspiratory apnea.86 Electrokymography is of less help than in cases of mitral insufficiency in spite of the ease with which right atrial tracings are recorded. 15 Right heart catheterization confirms the presence of incompetency by revealing a plateau pattern within the right atrial cavity.86 An abrupt change usually takes place as soon as the catheter is withdrawn to the axillary vein (venous valve).87 The frequent existence of "relative" tricuspid insufficiency with signs which cannot be easily distinguished from those of organic insufficiency somewhat detracts from the value of these data. Therefore, these should be considered as probatory only if right heart failure can be excluded (lack of typical symptomatology; no increase in the diastolic pressure of right ventricle).

Tricuspid stenosis is more difficult to diagnose. A diastolic rumble or an opening snap can frequently be auscultated and recorded at the right of the sternum. If present, they increase in inspiration, a fact which is not true in the case of a mitral diastolic murmur or snap. Jugular and tricuspid tracings reveal a high atrial, presystolic wave in cases with a sinus rhythm. 88,89 Unfortunately, other conditions which increase right ventricular strain may present the same pattern and, moreover, atrial fibrillation frequently

complicates tricuspid stenosis. Cardiac catheterization reveals that mean atrial pressure is higher than the end diastolic pressure of the right ventricle.⁹⁰

Tricuspid insufficiency and stenosis give the signs and symptoms of both lesions. The plateau of the venous and hepatic tracings is less high and more delayed; 85 the pulsations of the jugular veins are less marked than in pure insufficiency.

PULMONIC VALVE LESIONS

Rheumatic lesions of the pulmonic valve are extremely rare. They are occasionally encountered in patients with lesions of the other three valves (four-valve defects). On the other hand, patients with mitral valve involvement may present a loud, harsh, early diastolic murmur over the second left interspace and it may be important to ascertain whether this murmur is due to aortic or pulmonic insufficiency. Pulmonic insufficiency may be the result not only of persistent high pressure in the pulmonary artery, with fibrosis of the leaflets, but also of scarring subsequent to rheumatic valvulitis. The clinical, graphic and roentgenologic data which can be used for diagnosis were discussed in a previous paper.92 Electrokymographic comparison between the pulses of the aortic and the pulmonic knobs83 supplies additional valuable data.

SUMMARY

The diagnosis of rheumatic heart disease requires recognition of the etiology of the process and evaluation of myocardial, endocardial and pericardial lesions, as well as of possible lingering activity of the rheumatic process. The question whether the patient is a rheumatic at all may often be answered by history and physical examination. The presence of myocardial damage is frequently determined by study of the electocardiogram. Various laboratory tests and the clinical picture are of help in the diagnosis of active rheumatic carditis. Pericardial adhesions are likely in patients with a history of pericarditis. However, constrictive pericarditis of rheumatic etiology is extremely rare.

Murmurs should be evaluated carefully (1) because children and adolescents may present systolic murmurs of undetermined nature, possibly innocent and (2) because rheumatic carditis may cause not only an apical or pulmonic systolic murmur but also an apical middiastolic or presystolic murmur. The differential

diagnosis between the apical diastolic murmur of mitral stenosis and that of "relative" stenosis caused by carditis is aided by phonocardiography.

The differentiation between "pure" mitral stenosis and mitral insufficiency plus stenosis may be necessary in relation to possible surgical repair of the valve. The following diagnostic methods are briefly reviewed: (1) Physical examination and low frequency tracing, (2) auscultation and phonocardiography, (3) electrocardiography and vectorcardiography, (4) ballistocardiography, (5) pressure tracings of the left atrium, (6) esophagocardiograms, (7) roentgenograms and roentgenkymograms, (8) electrokymograms. In general, "pure" insufficiency or stenosis is recognized without difficulty by means of physical data plus electrocardiography, phonocardiography and roentgenology. On the other hand, demonstration of associated mitral insufficiency in a case of mitral stenosis may be difficult and use of the various subsidiary diagnostic methods may be necessary.

A ventricular pressure pattern (positive plateau-like wave) is transmitted to the left atrium in cases of mitral insufficiency. Esophagocardiography, roentgenkymography, electrokymography, direct measurements of atrial pressure and digital exploration permit recognition of this abnormal pressure wave which causes systolic expansion of the atrium. Electrokymography is the simplest of the five procedures. While it is a valuable diagnostic method (technical failures are discussed; personal data are given), it tends to overemphasize the disturbance although calibration and analysis of the tracings may remedy this. Digital exploration tends to underestimate the insufficiency, for reasons given. Therefore, if technical difficulties can be surmounted, pressure measurements with closed chest and no anesthesia may become the most accurate method.

The various technical aids for diagnosis of an associated aortic, pulmonic or tricuspid defect are discussed.

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The Treatment of Rheumatic Fever*

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THERE are many time-honored measures of assured value in the treatment of rheumatic fever which will not be considered in any detail in this discussion because their usefulness is too well established to require it. These measures include rest, salicylates for polyarthritis and fever, and digitalis and mercurial diuretics for congestive heart failure if it occurs. For the purposes of this symposium attention will be directed to those important aspects of treatment which are new or about which there is still difference of opinion. These are: (1) the use of penicillin in treatment (in addition to its great proven value in preventing rheumatic fever), (2) the value of cortisone and corticotropin and (3) the possible beneficial effect of salicylates on carditis.

USE OF ANTIBIOTICS

Within a few years of the introduction of sulfonamides in therapy this group of drugs was tried in rheumatic fever. Their enormous value, and the still greater value of penicillin, in the prophylaxis of rheumatic fever was quickly shown. ¹⁻³ On the other hand, sulfonamides were found to be without benefit in established rheumatic fever and, indeed, for a time were actually thought to be harmful. ^{4,5} Subsequent experience has indicated that sulfonamides and penicillin do not cause rheumatic fever to worsen and, hence, their possible value in eliminating the hemolytic streptococcal carrier state became an important issue.

It has been shown that sulfadiazine will prevent hemolytic streptococcal infections but cannot be relied on to eliminate completely hemolytic streptococci which the patient may already harbor. Penicillin, on the contrary, can eliminate the hemolytic streptococcal carrier state and is, therefore, the drug of

choice for this purpose. A number of satisfactory dosage schedules are available, including the following: (1) oral penicillin may be given in doses of 250,000 units twice daily for a period of ten days; (2) procaine penicillin in oil with 2 per cent aluminum monostearate may be given in doses of 600,000 units intramuscularly every second day for four doses; or (3) benzathine penicillin G may be given as a single intramuscular injection of 1,200,000 units. Any one of these methods will eliminate the carrier state in all but the rarest exceptions. No published reports are as yet available comparing end results of therapy which includes measures to end the carrier state with the results of regimens not including those measures. However, there is every reason to believe that hemolytic streptococcal infection can maintain as well as initiate rheumatic attacks and, therefore, on theoretic grounds it would appear to be important to take early and adequate measures to eradicate any viable hemolytic streptococci which the patient may carry.

The importance of preventing hemolytic streptococcal infections in patients who have recovered from rheumatic fever has been established without question. For the reasons already noted, it must now be considered imperative also to start the prophylactic regimen just as soon as the measures to eliminate any possible hemolytic streptococcal carrier state have been completed. For this continuous prophylaxis a number of methods are available which are discussed in detail by Stollerman.1 Schedules which may be recommended include: (1) oral penicillin in doses of 250,000 units once daily, preferably half an hour before breakfast: (2) benzathine penicillin G intramuscularly in doses of 1,200,000 units every four weeks; and (3) sulfadiazine by mouth once daily in doses

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of 0.5 gm. for small children and 1.0 gm. for patients weighing over 100 pounds.

CORTISONE AND CORTICOTROPIN

Since the original report of Hench and his collaborators⁵ in 1949, ample experience has accumulated to establish beyond question the effectiveness of cortisone and corticotropin in combating the polyarthritis, fever and general toxic state of the acute phase of rheumatic fever. Because of these striking effects and especially because of early reports of resolution of rheumatic subcutaneous nodules, which have notoriously been considered to be unaffected by salicylates, the hope was raised that in cortisone and corticotropin there were at last available agents which could control carditis. Soon reports of treatment began to appear, but always in small numbers of patients and with very discordant results. A few authors have reported very encouraging results. 6-12 Others, on the contrary, have found the hormones no more effective than salicylates, or frankly disappointing, 13-19 while the majority 20-34 have considered them promising but of still unproved benefit in carditis. Because of the great importance of the subject and the difficulty of accumulating a statistically significant group of patients in any one clinic, an international cooperative study of the comparative effects of acetylsalicylic acid, cortisone and corticotropin in rheumatic fever was undertaken in 1950 by thirteen clinics in the United States, Canada and England with the sponsorship of the American Council on Rheumatic Fever and Congenital Heart Disease, the National Heart Institute and the British Medical Research Council. Although the preliminary results of this study have been reported at the meeting of the American Rheumatism Association in Chicago in 1952 and at the International Congress on Rheumatic Diseases in Geneva in 1953, and a full report is now in preparation, only the briefest published report has thus far been made.21 This report may be summarized by the statement that little difference was found in the results obtained with these three therapeutic agents. This can mean that all three are of essentially equal value in rheumatic carditis, that none is of value or that the plan of the study was imperfect. In the study, for example, a rigid schedule of amount and duration of dosage for each of the agents was adhered to, and the objection has been raised that sufficiently large doses of cortisone and corticotropin

may not have been employed to suppress cardiac inflammation in the more seriously sick patients. Thus Greenman, Weigand and Danowski, 14 using far larger doses of 300 mg. daily for six to eight weeks, reported favorable results in patients treated relatively early. In their series ten of twelve children with carditis who were treated within two weeks of onset of rheumatic fever recovered without residual cardiac damage, and similar promising results have been observed by our Study Group at Bellevue Hospital* in seven patients with carditis treated early in their first attacks with the same large doses.35 The serious weakness of all these individual impressions of benefit, however, is the fact that they are based on such small numbers of patients that they are not satististically sound. It must be noted too that in contrast to those who advocate large doses are the reports of Wilson and her associates.6 These authors gave relatively small doses of corticotropin for only seven days to twenty-four patients who were considered to have active carditis of less than nineteen days' duration and reported prompt termination of carditis in all without residual cardiac damage. These results have not been supported, however, by the experience of any other investigator.

In this incomplete and unsatisfactory state of knowledge regarding the over-all value of cortisone and corticotropin in rheumatic fever it is helpful to consider their effects on the individual manifestations and symptoms of the disease. In the paragraphs which follow this is done in summary form. For a detailed analysis of results of therapy in the various manifestations the reader is referred to the excellent review of the literature recently compiled by Massell.³⁶

Polyarthritis, Fever and Toxic State. As has already been noted, there is no doubt about the beneficial effects on the polyarthritis, fever and general toxic state induced by rheumatic fever. Doses of 25 mg. of cortisone by mouth four to six times daily cause dramatic relief of all of these within twelve to forty-eight hours but it must be borne in mind that full doses of salicylates (of 0.06 gm. per pound of body weight) will accom-

^{*} The members of the Study Group who participated in these observations and others referred to throughout this paper included: from the Department of Pediatrics, Drs. Janet S. Baldwin, Ann G. Kuttner and Eugenia F. Doyle; from the Department of Medicine, Drs. Currier McEwen, Joseph J. Bunim (now at the National Institute of Arthritis and Metabolic Diseases) and Morris Ziff.

plish essentially the same results. Indeed, when cortisone is given intramuscularly the effects are less dramatic than those achieved with salicylates because of the slower absorption of the hormone when given by that route.

Subcutaneous Nodules. In spite of early reports of rapid disappearance of subcutaneous nodules under therapy with cortisone or corticotropin,8. ^{22,27} more recent studies comparing the effects of these hormones and of salicylate in rheumatic subjects20,21,32 have reported little or no difference between the effect on nodules in the three treatment groups and also an increase in nodules in some of the patients in each group. It appears clear that nodules may increase in size or in number or, indeed, appear for the first time while the patient is receiving these hormones. On the other hand, most observers have gained the strong impression that these lesions do resolve more rapidly under adequate cortisone therapy than would be expected spontaneously. The question is of small importance, of course, so far as the nodules themselves are concerned but considerable theoretic interest attaches to the issue because of the indirect bearing on the value of hormone therapy in carditis. If the subcutaneous granuloma is influenced by cortisone, it would be reasonable to hope for a similar effect on the proliferative as well as on the exudative phase of inflammation in the heart. The question is similar to that in the case of the subcutaneous nodules of rheumatoid arthritis. There seems little doubt that nodules disappear in a striking way in some rheumatoid patients, yet in others no effect is discernible.37 Why these differences exist, if indeed they do, remains unexplained although it is possible that dosage is a factor.

Histologic examination of rheumatic subcutaneous nodules also has led to conflicting findings. Nodules were removed from one of the patients studied by our group before and thirtyeight days after the start of hormone therapy.29 In the small residual nodule masses of fibrinoid material appeared to be as abundant as in the nodule excised before therapy, but the cellular elements, so abundant in the latter, were almost entirely absent in sections from the second nodule. Keith and Neill33 have also reported a decrease in inflammatory changes in a nodule removed after three weeks of hormone therapy. On the other hand, Bywaters and Dixon³² and Johnson and his associates18 reported no differences in nodules removed before and after

hormone therapy. Possibly these discrepant results are explainable on the basis of differences in dosage or length of treatment but it is clear that additional study is needed to clarify the question.

One may summarize the current state of knowledge regarding the effect of cortisone and corticotropin on rheumatic subcutaneous nodules by the statement that although a final decision is not yet justified, it is probable that these lesions are influenced favorably.

Chorea. The opinions of various authors on the efficacy of cortisone and corticotropin in chorea also differ. Massell, ³⁶ in an analysis of twenty-six cases gathered from published reports, found that 69 per cent recovered within four weeks of the start of hormone therapy. This is in contrast to the finding of Sutton and Dodge³⁸ who reported that only 22 per cent of 150 patients with chorea, treated before the era of cortisone, recovered within that period of time.

Our group at Bellevue Hospital has studied twenty-two children with chorea since 1950, of whom seventeen had no other rheumatic manifestations and five had both polyarthritis and carditis in addition. In thirteen of these patients hormone therapy was considered to be of benefit, in four the effect was questionable and in five no benefit was observed. Of the latter, involuntary movements became worse in one in spite of cortisone started after two weeks of chorea in doses of 300 mg. the first day, 200 mg. the second day and 100 mg. daily for the next five days. In two of the patients with good responses chorea diminished markedly while cortisone was being taken, increased when the hormone was stopped and again subsided when treatment was resumed. Thus, while present information does not permit a definite conclusion, there is suggestive evidence that chorea may be influenced by hormone therapy in some patients. Of interest in this connection are the earlier reports of Sutton and Dodge³⁸⁻⁴¹ on artificially induced fever therapy. In the light of current knowledge it may be that the benefit reported in their patients was due to adrenal cortical stimulation induced by fever therapy.

Erythema Marginatum. Although the mechanism of production of erythema marginatum in rheumatic fever is not understood, it is so characteristic a feature of the disease that it is usually considered a rheumatic manifestation. Reports of benefit induced by cortisone or corticotropin vary greatly, as summarized in Massell's

review.³⁶ In the patients studied by our group erythema marginatum has sometimes continued or even appeared for the first time during intensive therapy with cortisone. In other patients a rash present before treatment cleared promptly when cortisone was begun. However, the evanescent nature of these lesions in untreated patients makes it difficult to judge whether their disappearance was spontaneous or the result of therapy.

Carditis. The effect of cortisone and corticotropin on carditis is, of course, the really basic question and, in the current state of incomplete information, can perhaps be best discussed by considering separately the various manifestations of rheumatic inflammation of the heart.

So far as pericarditis is concerned the problem is made difficult by the transient nature and variable duration of the manifestation in untreated patients. 42 In his summary of reported cases Massell³⁶ has tabulated the results in sixty-four patients collected from the literature, in eighty four per cent of whom evidence of pericarditis disappeared during hormone therapy. In thirtyfour of these patients the duration of pericarditis was recorded. In twenty-four it cleared within seven days of treatment, in nine it cleared in eight to fourteen days and in only one did it persist more than two weeks. In four additional patients it appeared for the first time or persisted during treatment and in six it persisted up to the time of death. Some of the latter ten cases, however, cannot be accepted as failures either because dosage was small or hormone was given only a few days before death occurred. Obviously, interpretation of the benefit given by the hormones depends on what the natural duration of pericarditis in these patients might have been. Obviously, too, this cannot be answered, but the results in these collected cases plus the experience of many investigators treating individual patients strongly supports the probability that cortisone and corticotropin in adequate doses do benefit acute rheumatic pericarditis. It should be noted also that almost all investigators have agreed that electrocardiographic evidence of pericarditis usually persists days or weeks longer than the clinical signs.

When tachycardia occurs together with high fever in the acute phase of rheumatic fever, a dramatic slowing may be expected to occur following the administration of cortisone or corticotropin, which tends to parallel the fall in fever. Tachycardia not associated with high fever, such

as that seen later in the attack and usually thought to be due primarily to myocardial damage, shows a far less striking or uniform response. In the patients studied by our group there has been in general a gradual decrease in tachycardia but, on the other hand, in some patients with carditis (five of sixty-two) tachycardia persisted without any obvious effect from even large amounts of hormone. It must be emphasized, however, that all five of these patients had long-standing carditis in the subacute and chronic stage by the time hormone was begun.

Like tachycardia, gallop and changes in the quality of heart sounds have tended to clear in the patients studied by the author, but in some little or no benefit has been noted. This has been observed especially in those patients in whom tachycardia also continued. However, interpretation of changes in gallop and in quality of heart sounds is so dependent on subjective factors that we have made no attempt to analyze them quantitatively.

One of the most obvious evidences of severe carditis and one relatively easy to measure is congestive failure. Massell36 collected from the literature a total of forty patients with congestive failure who were given cortisone or corticotropin and of whom thirty were much improved. Among the patients with carditis whom we have studied eight had congestive failure. Of these, failure cleared rapidly during hormone therapy in five without the addition of digitalis or diuretics. In the other three patients these additional measures were required. One was a nine year old child treated in 1949 before we recognized the need to restrict the salt intake drastically. In a second child cortisone was given in amounts we would now consider insufficient; and in only one patient maintained on a diet containing less than 50 mg. of sodium daily and given adequate amounts of cortisone were digitalis and diuretics needed. This two and onehalf year old child entered the hospital critically ill on the fourteenth day of a first attack of rheumatic fever. None of the eight physicians who followed the course of illness in this child can escape the belief that cortisone was a lifesaving measure in this case. This, of course, is not subject to proof, but in the series of sixty-two patients treated there have been two so seriously ill that we believe they could have been expected to succumb without hormone therapy.

The possible effect of cortisone and corticotropin on cardiac enlargement is particularly

difficult to evaluate because of the role pericardial effusions may play. In some case reports, for example, it is probable that what has been interpreted as decrease in enlargement has been due to absorption of pericardial effusions. Furthermore, the question is complicated by the enlargement caused in some patients, whose salt intake has not been sufficiently restricted, by the accumulation of tissue fluid and increase in blood volume. In Massell's36 review of the literature data are presented which suggest that decrease in cardiac enlargement may depend importantly on the duration of disease when hormone is begun. Thus in seventeen patients with enlargement in whom no evidence of pericarditis was found and in whom hormone therapy was begun within forty-two days of illness, enlargement decreased or disappeared entirely in thirteen; whereas in thirteen similar patients in whom treatment was begun more than forty-two days after onset, decrease in heart size occurred in only one.

The effect of hormone therapy in preventing cardiac valvular damage as shown by changes in murmurs is difficult to assess because of the subiective factors involved, especially in interpreting the significance of systolic murmurs. It can be said with assurance that established murmurs resulting from damage incurred in previous attacks are not affected by hormone therapy. Furthermore, Massell's analysis of reported cases³⁶ gives support to the view that the end result of murmurs appearing during current attacks depends on how early in the attack therapy is started. Thus, of 120 murmurs which appeared in initial attacks of rheumatic fever, the rate of disappearance was 94 per cent in twenty patients treated within seven days of onset of the attack, 52 per cent in twenty-seven patients in whom treatment was started between the eighth and fourteenth day of disease, 28 per cent in twenty-two patients in whom treatment was started between the fifteenth and twenty-eighth day of disease, 19 per cent in sixteen patients in whom treatment was started between the twentyninth and forty-second day of disease, and only 6 per cent in thirty-five patients in whom treatment was begun later than the forty-second day of illness. Analysis of Massell's collected cases from the standpoint of the presence of murmurs at the end of treatment36 revealed that of thirtyone patients with initial attacks of one to seven days' duration at the start of treatment only 6.5 per cent were left with significant murmurs,

whereas this figure rose progressively to 49 per cent of thirty-five patients treated between the eighth and fourteenth days, 66 per cent of thirty-three patients treated between the fifteenth and twenty-eighth days, 75 per cent of twenty patients treated between the twenty-ninth and forty-second days, and 90 per cent of forty patients treated after the forty-second day.

The patients studied by our group since 1949 number ninety-four children and ninety adults, of whom fifty-three children and thirty-five adults had definite evidence of carditis. Yet the number of these whom we consider suitable for drawing conclusions regarding the fate of murmurs is small. In 1949 when our observations were begun we hoped to get a quick answer to the question of whether cortisone and corticotropin could suppress rheumatic inflammation in the heart by treating patients with advanced rheumatic heart disease and active carditis. The futility of this approach was soon apparent and since that time we have been primarily interested in patients with definite carditis in whom treatment could be started within the first fourteen days of their first attacks, but these cases are not numerous. In preliminary studies six such patients, all under ten years of age, received varying doses of corticotropin, or three days of corticotropin followed by cortisone, or cortisone alone. The maximum daily dose of corticotropin was 60 mg. maintained for three days and of cortisone, 200 mg. maintained for four days. The doses then were gradually reduced over additional periods of thirty-three to forty-two days. Only one of these six children in whom treatment with moderate doses was started within the first two weeks of illness was judged to have a normal heart at the end of treatment. Three had apical systolic murmurs considered indicative of mitral insufficiency and two had apical diastolic murmurs in addition to systolic murmurs. The cardiac status of these six children has not changed over a one- to four-year period of follow-up.

During the past two years six similar children and one girl of eighteen, all within the first two weeks of illness, were treated with prolonged high dosage of cortisone or hydrocortisone (300 mg. daily) for thirty-two to forty-two days. Five of these seven have left the hospital with no evidence of organic heart disease. One child had a harsh apical systolic murmur and one an aortic diastolic in addition to a systolic murmur. Certainly these cases are too few to warrant the

conclusion that the larger doses are superior to the smaller ones, but the second group of patients was even more severely ill than the earlier group and the results are at least suggestive.

Finally, in the consideration of possible effects of cortisone and corticotropin in carditis, there is the question of electrocardiographic changes. It has already been mentioned that electrocardiographic changes in pericarditis do not revert to normal as rapidly as do the clinical signs of pericarditis. Prolongation of the P-R interval usually has been observed to return to normal within a week of starting hormone therapy but this, of course, is a common occurrence in untreated patients. More suggestive of the effect being due to the therapy used are the instances of return of the prolongation when hormone was stopped and shortening again with reinstitution of therapy. However, even these instances could be coincidental in a phenomenon as variable and subject to rapid changes as the P-R interval in rheumatic fever.

Effects on Erythrocyte Sedimentation Rate and on C-Reactive Protein. Of the various laboratory aids in following the degree of activity of the disease process in rheumatic fever, the two most important are the erythrocyte sedimentation rate and the C-reactive protein precipitin test. 43 It is now thoroughly established that both tests return to normal in two to four weeks under the influence of therapy with cortisone or corticotropin. Less certain, however, is the significance of these effects. There is little doubt that both phenomena are secondary to inflammatory changes and the most likely explanation of the return of erythrocyte sedimentation to normal and of the disappearance of the C-reactive protein is that these effects reflect hormone-induced suppression of the rheumatic inflammation. On the other hand, it has been suggested 44-46 that the fall in sedimentation rate may be due to direct changes brought about by cortisone in the plasma levels of fibrinogen, gamma globulin and other proteins. Of great practical importance, irrespective of which of these mechanisms is correct—and it may well be that both play a part-is the fact that the return of these tests to normal cannot be interpreted to mean that the underlying mechanism of rheumatic activity has become quiescent so long as the patient is receiving cortisone or corticotropin. One probably is justified in interpreting this to mean that inflammation has been suppressed, at least in part, but the only way to

discover whether the underlying disease process has become inactive is to reduce dosage of hormone cautiously and see if laboratory or clinical evidence of continuing rheumatic activity reappears.

The Rebound Phenomenon. The reduction of hormone dosage just mentioned leads naturally to a discussion of the "rebound phenomenon," as the flurry of signs and symptoms of rheumatic activity which is apt to appear at such times usually is called. On occasion, if the underlying rheumatic fever is definitely active, removal of the suppressing effect of the hormone will be followed by a full-blown rheumatic recrudescence. If, however, hormone has been continued sufficiently long for the disease to be below the level of recognizable activity, the rebound is apt to occur. This consists of transient increase in sedimentation rate and reappearance of the C-reactive protein coupled sometimes with mild rise in temperature and pulse with or without arthralgia or other mild symptoms or signs of rheumatic fever. This flurry persists for a few days and then gradually subsides. The mechanism of this phenomenon is not understood. A reasonable explanation at first was that it reflected an increased sensitivity of the patient to residual and minimal rheumatic stimuli during a time when exogenous cortisone or corticotropin was no longer available and the patient's intrinsic adrenocortical hormones had not yet taken its place. However, in a few observations in our laboratory Dr. Hildegard Wilson has found no changes in ketosteroid or 11-oxysteroid excretion at the time of the rebound.47 Furthermore, it now appears clear that salicylates do not exert their antirheumatic effects through an adrenocortical mechanism, 48,49 yet Fischel, Frank and Ragan⁵⁰ and others have observed characteristic rebounds in rheumatic patients treated with salicylates when the latter were discontinued. At the moment, therefore, while it is easy to explain frank rheumatic relapses occurring when cortisone or corticotropin is withdrawn, the mechanism of the rebound is obscure. From the practical standpoint, however, it is important to bear the phenomenon in mind lest hormone therapy be resumed unnecessarily in the mistaken idea that a true recrudescence of rheumatic fever has occurred.

Undesired Effects. The frequency with which undesired effects occurred in our first forty-four patients, aged two to twenty years, with rheumatic fever treated with these hormones is shown in Table 1. Our experience has been essentially the same in the additional patients treated since that time. However, in the group of patients given the large doses of 300 mg. of cortisone daily, moonface and obesity were constant.

TABLE I

INCIDENCE OF TEMPORARY, UNDESIRED EFFECTS IN FORTY-FOUR PATIENTS WITH RHEUMATIC FEVER (AGES TWO TO TWENTY YEARS) DURING HORMONE THERAPY

HORMONE THERAPY		
Moonface	 	 38
Abnormal fat deposits	 	 23
Acneform eruption		
Hirsutism		12
Striae	 	 8
Peripheral edema	 	 7
Liver enlargement (without congestive failure)		6
Abdominal distention		6
Pigmentation	 	6
Tremors		4
Furunculosis		 4
Glycosuria (trace)		3
Insomnia		2
Hypopotassemia		2
Petechiae		1
* All patients were under the age of eight ye		

Serious effects have occurred relatively infrequently. One sixteen year old girl became mildly psychotic but this condition cleared with electric shock therapy. However, it should be remarked that she had been a behavior problem at home long before her illness. In three children hormone therapy had to be stopped because of the development of hypertension with diastolic pressures above 100 mm. One of these children received cortisone in doses of 300 mg. daily and the other two hydrocortisone in the same dosage. The blood pressure returned to normal in two to four days in all when hormone was stopped. Peptic ulcer occurred in none and glycosuria was a very minor problem.

Two effects which deserve special mention although they are not serious are pigmentation and liver enlargement. In some patients the pigmentation in its early stages has suggested cyanosis. The liver enlargement also can be misinterpreted as due to heart failure unless it is recognized that fatty infiltration can occur. 51 Both these effects subside when the hormone is stopped.

VALUE OF SALICYLATES IN CARDITIS

Although some European writers have long held that salicylates have a curative effect on rheumatic carditis, workers in this country and

in England have been almost universally of the opinion that, in spite of their dramatic effect on fever and polyarthritis, these drugs have little if any direct beneficial effect on carditis. It has been thought that, indirectly, some benefit probably results from the slowing of the heart rate accompanying the salicylate-induced fall in fever, but the many documented instances of progressive heart damage and the appearance of acute pericarditis in patients on full therapeutic doses of salicylates have made it seem unlikely that the well known antirheumatic action of these drugs on the polyarthritis of rheumatic fever is effective also in carditis.

Paradoxically, it has been the cooperative study of the value of cortisone, corticotropin and salicylates in rheumatic fever¹⁹ which has raised anew the question whether salicylates may not, after all, exert a beneficial effect on the heart lesions. In the minds of most American students of the disease it has been so firmly fixed that salicylates do not benefit carditis that it has been a surprise to find that in a carefully conducted analysis of a large number of patients, those who received salicylates fared about as well as those treated with cortisone or corticotropin. 19 At the same time the evidence that those hormones do exert a beneficial effect when given early in carditis has led to the obvious conjecture that perhaps salicylates too may be of help.

Unfortunately, few recent data bearing on this question have been reported. Fischel, Frank and Ragan⁵⁰ have shown that rebounds similar to those seen following the rapid withdrawal of cortisone or corticotropin occur following the rapid withdrawal of salicylates. Furthermore, Fischel⁵² has reported that the rebounds of cortisone and corticotropin withdrawal can be suppressed or minimized by the administration of salicylates during and after the reduction and cessation of hormone. Similarly, Fischel⁵² and other clinicians in this country and abroad 53,54 have tried combined cortisone and salicylate therapy, with what they have considered en-

couraging results.

The subject of the possible use of cortisone and salicylate simultaneously poses the important theoretic question whether the therapeutic effect of salicylates is not due to stimulation of the adrenal cortex. Some evidence favoring such an action has been reported in animals 55-58 but only with doses of salicylate so large as to be capable of causing stress. More physiologic studies in animals and in man48,49,59 do not bear

out the contention of common action, and it is significant that even large (but non-toxic) doses of salicylates administered to patients over periods of months do not cause "moonface" or other signs of hypercorticalism. The weight of evidence is heavily against a common mechanism of therapeutic action for salicylates and cortisone, and, hence, there is theoretic justification for combined therapy. Certainly it is not possible to say with complete confidence today that cortisone and corticotropin are of benefit in carditis; and the value of salicylates in this sense is even less certain. However, in the present state of knowledge it is the author's opinion that it is unjustifiable not to give cortisone or corticotropin in large doses to a patient with carditis; and furthermore, that there is sufficient evidence in favor of a beneficial action of salicylates to warrant the combined use of these drugs with hormone therapy.

A SUGGESTED PLAN OF TREATMENT

Based on the principles which have been discussed previously, a plan of treatment may be suggested as follows:

- In any patient with rheumatic fever, penicillin should be given at once in sufficient doses to eradicate the hemolytic streptococcal carrier state.
- Prophylaxis should then be begun and continued indefinitely to prevent further infection with hemolytic streptococci.
- 3. If there is no evidence of carditis, salicylate alone probably is preferable to hormone therapy. For this purpose a satisfactory dosage schedule for acetylsalicylic acid is 0.06 gm. (1 gr.) per pound of body weight (up to a maximum of 10 gm.) daily for two days, then 0.04 gm. (2_3 gr.) per pound daily for five days and 0.03 gm.(1/2 gr.) per pound daily for three weeks. After this salicylate can be reduced 1 gm. daily, provided the C-reactive protein has disappeared from the blood and does not return, save for a possible transient "rebound" after salicylate has been discontinued. If C-reactive protein has not disappeared by the end of four weeks it is highly probable that the patient has smoldering carditis and cortisone probably is indicated. Giving the salicylate in divided doses of 1 gm. (15 gr.) each appropriately spaced through the day is less apt to lead to acute salicylate toxicity than are larger doses given at wider intervals.
- 4. In the presence of carditis we believe cortisone should be started at once in doses of 300 mg.

daily by mouth. This is continued for six weeks, after which the dose is reduced half a tablet (12.5 mg.) daily. Because of the salt-retaining effect of cortisone when given in doses of this size a rigid diet containing less than 50 mg. of sodium daily is imperative. To counteract the possibility of potassium depletion, potassium chloride in enteric-coated tablets is given in doses of 1.0 gm. two or three times daily after meals. While six weeks of cortisone usually suffice, further treatment is indicated if the C-reactive protein is still present. A transient "rebound" when hormone is stopped does not call for further treatment. However, if a true relapse occurs or if clinical or laboratory evidence of continuing low grade carditis persists, cortisone should be resumed.

5. If salicylate is to be given together with cortisone, the dosage may be as outlined above. However, on theoretic grounds, in the hope of minimizing the rebound phenomenon, it would seem advisable to continue salicylate dosage at the level of 0.03 gm. per pound of body weight daily for three weeks after cortisone has been stopped.

SUMMARY

The treatment of rheumatic fever has been discussed in the light of current information regarding the use of antibiotics, cortisone and corticotropin, and salicylates.

The importance of eradicating any possible hemolytic streptococci which the patient may carry by means of adequate doses of penicillin appears to be unquestionable, as is the need for continued prophylaxis against further infections with hemolytic streptococci.

Although the value of cortisone and corticotropin in rheumatic carditis is not yet established beyond question, the evidence to date is encouraging, especially when therapy can be started within a few days of onset of illness. These hormones appear to be of little if any benefit in long-standing subacute and chronic carditis.

The value of salicylates in carditis is still less clear, but the meager evidence available is sufficiently hopeful to warrant the combined use of this drug with cortisone.

For the treatment of rheumatic polyarthritis without evidence of carditis, salicylate probably is preferable to cortisone or corticotropin.

A plan of treatment employing these agents has been outlined.

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The Selection of Patients for Mitral Commissurotomy*

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has passed through its pioneer phase and has emerged as a reasonably satisfactory procedure permitting direct surgical relief of mitral stenosis. With good surgery and proper medical evaluation many patients have been much improved. Observers with the greatest experience readily agree on this point, although everyone is aware that reports have of necessity been based on observations limited to periods of a few years. So far one can only state that mitral commissurotomy is capable of producing short term improvement, and no one knows how long such improvement will be maintained.

The internist, who formerly concerned himself with standard medical methods of treatment, now must also know how and when to select from among his patients those suitable for surgery, join in the medical aspects of their preoperative preparation and immediate postoperative care, and later supervise their longterm management.

This discussion will deal only with the selection of patients for mitral commissurotomy. The material presented is based on personal experience in the evaluation of approximately 400 patients with valvular heart disease referred as candidates for surgery. Others have similarly summarized their experiences and representative reports from various centers are listed in the references. 1-3.5

During the past five years concepts regarding the selection of patients have undergone constant revision as a result of increasing experience of both surgeon and internist. The present report represents current views and also is "subject to change without notice." For example, many of the present difficulties would vanish in the event of a major improvement such as a satisfactory technic for mitral surgery under direct vision. Pending a development of this magnitude, many of the problems considered here will continue to be important.

GENERAL CONSIDERATIONS

Basically, decisions as to any form of surgery should be reached by first balancing the estimated risk and anticipated benefits of the contemplated surgery against those of conservative management, and then choosing the method of treatment considered best for the individual patient. In the selection of patients for mitral commissurotomy the factors requiring consideration are subject to unusually wide variation for the following reasons: (1) Uncomplicated mitral stenosis may pass through several stages of different hemodynamic significance. This of itself leads to variability both in the risk and in the results of surgery. (2) The course of this disease can be complicated and modified by a number of special developments such as embolism and arrhythmia. (3) Patients with mitral stenosis frequently have superimposed disease of other valves of varying degrees of importance.

The surgical risk will thus differ from patient to patient depending on the stage of the disease and the presence or absence of complicating factors. The risk will also vary greatly with the experience of the surgeon; most reports have shown higher mortality rates for the first twenty-five or fifty cases than for subsequent increments of a given series. Naturally, the risk is increased in patients with advanced disease and long-standing congestive failure. Under the best of circumstances the mortality rate is 3 to 5 per cent in the "better risk patients." This figure rises in proportion to the number of "poor risk" patients accepted for surgery.

The chances for improvement following surgery are similarly subject to variation. In gen-

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eral, it may be said that results are favorable in patients with uncomplicated mitral stenosis but that the presence of far advanced congestive failure or of complicating valvular lesions reduces the likelihood of improvement.

In view of these considerations, the subject of selecting patients for mitral commissurotomy is not readily presented in the usual manner of listing indications and contraindications. Rather, it seems better to begin with a review of the pathologic physiology and natural history of mitral stenosis. From this evolves a simple classification which makes it easier to estimate the expected results and risks of surgery in patients with uncomplicated mitral stenosis. Finally, various complicating factors will be listed and each will be discussed from the point of view of its special importance in the selection of patients for mitral commissurotomy.

PATHOLOGIC PHYSIOLOGY

In a certain number of patients with rheumatic heart disease the major pathologic change consists of progressive stenosis of the mitral valve. Such patients are said to have "pure" mitral stenosis because there is no significant degree of mitral insufficiency, the other valves remain intact and the myocardial integrity has been preserved. By itself the mitral obstruction results in increased pressure within the left atrium which is reflected also as an elevation of pulmonary venous pressure. This chain of events commonly leads to a disturbance of the pressure relationships throughout the lesser circulation and eventually can cause symptoms due to pulmonary congestion, such as dyspnea, cough, orthopnea, paroxysmal nocturnal attacks, pulmonary edema and hemoptysis. Those patients who develop symptoms of pulmonary congestion usually notice them initially during severe exertion but later find that they occur with lesser degrees of physical activity, and finally are present even at rest. The natural progression of the disease may be so gradual that milder degrees of stenosis can be present for many years before the valvular narrowing is sufficient to cause troublesome symptoms. In addition, it is said that occasional patients seem to tolerate the disease unusually well and never develop significant disability despite a degree of stenosis apparently equal to that of many handicapped patients.

In many patients with "pure" mitral stenosis the disease advances beyond the stage in which the effects consist simply of pulmonary congestion due to interference with left atrial emptying. Instead, the prolonged pulmonary congestion apparently leads to pulmonary arteriolar vascular changes with marked pulmonary hypertension and severe adverse effects on the right ventricle. Such patients develop symptoms of so-called "right heart failure" including elevation of the peripheral venous pressure, hepatic enlargement and anasarca. In this stage the patient may also develop relative insufficiency of the pulmonic and tricuspid valves.

CLASSIFICATION OF PATIENTS

From the foregoing it can be noted that patients with predominant mitral stenosis fall into three major groups: (1) those without significant disability, (2) those with symptoms due to pulmonary congestion and (3) those whose disease has progressed to the stage of so-called "right heart failure." This rough classification is based entirely on the hemodynamic changes of uncomplicated mitral stenosis and does not include the modifying effects of various other factors present in numerous patients. However, it is useful for purposes of discussion and does provide a method for preliminary evaluation of patients from two basic aspects: first, their place in the natural history of the disease and second, the likelihood of surgical improvement at that stage.

Asymptomatic Patients. Most workers have hesitated to subject asymptomatic patients to mitral commissurotomy because the surgical risk is considered unjustified. Some dispute this viewpoint on the grounds that the risk is small and that these patients inevitably become disabled sooner or later. One must be certain of course that these patients really have no ill effects from their mitral stenosis. In some instances this decision is difficult because (1) certain of these patients psychologically reject their illness and will conceal or minimize their disability and (2) other patients have atypical symptoms which are not recognized as due to mitral stenosis. At present it seems wise not to subject truly asymptomatic patients to mitral commissurotomy when there is still at best a 3 to 5 per cent surgical mortality with the current technics.

The Ideal Patient. Experience has demonstrated that the best results from mitral commissurotomy occur in patients with "pure" mitral stenosis whose disease has progressed only

to the stage of pulmonary congestion. In many such patients technically successful surgical relief of mitral obstruction has resulted in restoration of practically normal circulatory relationships and apparent cure of the mitral stenosis. The ideal patient may be described as a young person, age thirty to forty years, who has progressive symptoms including exertional dyspnea, cough, orthopnea, paroxysmal nocturnal attacks, pulmonary edema or hemoptysis. The symptoms of so-called "right heart" failure are minimal or absent. The physical signs indicate "pure" mitral stenosis and include the characteristic loud apical diastolic rumbling murmur together with such associated findings as an opening snap sound, the typically "sharp" first heart sound at the apex and the accentuated or split second heart sound at the pulmonic area. Fluoroscopically the cardiac enlargement should not be excessive and should involve principally the left atrium and right ventricle. The electrocardiogram may be normal or may indicate the presence of "auricular abnormality" and "right ventricular predominance." Finally, the ideal patient does not show any evidence of rheumatic activity, significant mitral insufficiency or disease of other cardiac valves.

The Patient with Severe Congestive Failure. As might be anticipated, mitral commissurotomy has been less satisfactory in patients whose disease has advanced beyond the phase of pulmonary congestion and into the stage of socalled "right heart failure." In this group the surgical risk is increased while the chances for improvement are lessened. It is generally agreed that mitral commissurotomy is indicated if the congestive failure can be brought under control by medical therapy prior to operation, but a special problem arises in patients with severe "right heart failure" which persists despite intensive medical treatment. Formerly we were concerned that such patients might be inoperable because they presumably had irreversible pulmonary vascular changes. 6 However, some of these patients have survived operation and have improved. It is therefore possible that these supposedly irreversible organic changes may indeed be reversible. Thus the current tendency is to recommend mitral commissurotomy for these patients despite the high surgical risk and the relatively reduced chance for improvement. In a sense this approach constitutes "salvage surgery" similar to that in patients with cancer. Certainly before such an operation the patient's

family must be made to understand the exact situation and the patient should be told as much as seems indicated under the individual circumstances.

SPECIAL FACTORS AFFECTING THE SELECTION OF PATIENTS

So far the discussion has been confined to evaluation of patients based entirely on the hemodynamic effects of "pure" mitral stenosis. The selection of patients for mitral commissurotomy would be reasonably easy if this constituted the only problem. Unfortunately, the situation is frequently altered by the presence of various complications. It may be very difficult in some patients to determine whether their disability is due primarily to mitral stenosis or to other valvular disease. The following factors are discussed because, at various times, they require special consideration in reaching a final decision as to the operability of certain patients.

Age. The great majority of patients who develop disability due to "pure" mitral stenosis do so between the ages of thirty and forty-five. One rarely encounters disability due to purely mechanical mitral obstruction in patients under twenty years of age. Instead most teen-age patients with serious disability due to rheumatic heart disease prove to have complicating rheumatic activity, myocardial disease, severe mitral insufficiency, multiple valvular involvement, marked cardiac enlargement, or combinations of these. In the presence of such complications mitral commissurotomy would not be expected to produce real improvement. Our experience includes only two young patients (a boy of seventeen and a girl of fourteen) in whom the disability could be attributed entirely to severe mitral stenosis; both were greatly improved following surgery.

In patients over fifty years of age the surgical risk is increased. One must therefore be certain that older patients have serious progressive cardiac disability which is due to mitral stenosis and which cannot be managed effectively by medical measures. One must also try to exclude patients with other diseases of a serious nature so that successful mitral commissurotomy can be expected to promise a reasonable addition to the life span. Despite such considerations old age does not of itself constitute an absolute contraindication to operation in patients markedly handicapped by mitral obstruction. Extremely

gratifying results have been achieved in a number of older patients, including one aged sixty-two.

Rheumatic Activity. Most workers consider clinical evidence of active rheumatic fever or carditis as an absolute contraindication to mitral commissurotomy. The primary problem is the difficulty of recognizing such activity since it seldom manifests itself in any characteristic manner. In patients with rheumatic heart disease possible activity must be suspected in the presence of any vague-illness or with the development of such varied symptoms as fever, fatigue, malaise, anorexia or muscle pain. Sometimes the only manifestation is a sudden increase in the degree of cardiac disability. Various laboratory methods including special immunologic tests have not proved particularly helpful in this diagnosis. The most useful laboratory indication of activity may still be an increase in the sedimentation rate otherwise unexplained. Despite all efforts to exclude from operation those patients with active carditis, surgical biopsies of the left auricular appendage have shown Aschoff bodies in as high as 45 per cent. This has led to a controversy in which some workers have questioned whether Aschoff bodies in the left auricular appendage really indicate rheumatic activity. For the present most observers simply accept the finding as further evidence of the difficulty of recognizing rheumatic activity in this group of patients. So far our policy has been to avoid operation in the presence of clinically demonstrable rheumatic activity.

Apical Systolic Murmurs. One of the earliest principles governing the selection of patients for mitral commissurotomy was to exclude those with evidence of significant mitral insufficiency. Initially, the recognition of mitral insufficiency was based on clinical findings including the presence of an apical systolic murmur. As surgical experience increased it became obvious that the clinical estimation of the relative degrees of stenosis versus insufficiency frequently did not correlate well with the operative findings. Cardiac auscultation was found to be quite reliable in selecting those patients with so-called "pure" mitral stenosis who had loud apical diastolic murmurs but in whom apical systolic murmurs were either absent or faint. Auscultation, however, was particularly unreliable in evaluating the group of patients with prominent apical systolic murmurs; this finding does not guarantee the presence of significant mitral regurgitation. Often, despite a loud apical systolic murmur, the patient has proved to have severe mitral stenosis without significant insufficiency and has derived considerable benefit from mitral commissurotomy.

Experience has thus emphasized the inadequacy of ordinary methods of physical examination in the diagnosis of mitral insufficiency. Various special tests have therefore been used in an effort to recognize significant degrees of mitral regurgitation. Standard roentgenographic studies are not always helpful since it is frequently very difficult to estimate the size of the left ventricle, and the mere presence of a systolic pulsation of the left atrium visible fluoroscopically does not permit any estimation of the severity of mitral regurgitation. Cardiac catheterization has been used to record the so-called "wedge" pressures ("pulmonary capillary pressures") which are considered to reflect actual pressure relationships within the left atrium. This has helped us very little in the preoperative evaluation of patients. Combinations of phonocardiography, ballistocardiography and electrokymography have been used to provide data bearing on this problem. In our hands⁷ angiocardiography has supplied helpful information by showing a characteristic pattern of opacification for "pure" mitral stenosis of severe degree, and a different angiocardiographic pattern for "wide-open" mitral insufficiency. In "pure" mitral stenosis the left atrium remains sharply outlined and densely opacified for a long period of time whereas the left ventricle is poorly opacified and small. In severe mitral incompetence, on the other hand, the left atrium and left ventricle are opacified to equal degrees of intensity and the left ventricle is enlarged. This test has been particularly helpful in patients in whom the physical signs of mitral stenosis have not been typical. It has, for example, permitted recognition of mitral stenosis in a number of patients in whom no apical diastolic murmur was heard. Angiocardiography is of course most decisive when the pattern obtained is unequivocally that of mitral stenosis or that of mitral insufficiency. Unfortunately, the angiocardiographic pattern occasionally lies somewhere between these two extremes and decision may be difficult.

In no instance should a patient be rejected for operation merely because of the presence of an apical systolic murmur. All such patients deserve the benefit of special study, including an angiocardiogram, before a final decision is reached.

Aortic Valvular Disease. Earlier concepts regarding the significance of coexisting aortic valvular disease have undergone considerable change. Originally, any demonstrable disease of the aortic valve was considered an absolute contraindication to mitral commissurotomy. Aortic stenosis was doubly feared because (1) its obstructive effect was relatively greater following mitral commissurotomy and could cause failure of the previously "protected" left ventricle and (2) its preoperative recognition was often difficult in the presence of mitral stenosis. As one might expect, severe mitral obstruction can mask the presence of aortic stenosis by decreasing the intensity of the aortic systolic murmur. Certain patients with mitral stenosis have shown no definite aortic systolic murmur preoperatively, whereas after the mitral stenosis was treated surgically and blood flow through the left ventricle and aortic valve was increased a prominent aortic systolic murmur appeared. Aortic stenosis so missed occasionally has led to the death of a patient following an otherwise successful mitral commissurotomy. This is no longer so serious a problem since the development of an instrument for dilating stenosed aortic valves.8 The aorta should now be palpated routinely after mitral commissurotomy and if a significant systolic thrill is present the aortic valve should be dilated at the same operation. A potentially more reliable technic involves direct measurement of pressures within the left ventricle and aorta immediately following mitral commissurotomy. In aortic stenosis the aortic systolic pressure should be measurably lower than that within the left ventricle. As yet, however, the difference of pressure which indicates a degree of aortic stenosis requiring surgical treatment has not been determined. Aortic valvular dilatation in patients with isolated aortic stenosis carries a considerable surgical risk. However, in patients with tight mitral stenosis combined mitral and aortic surgery has resulted in a mortality rate of only about 10 per cent. The reasons for this difference in mortality between the two groups seem to stem from the fact that high grade mitral stenosis apparently "protects" the left ventricle from excessive hypertrophy. By contrast, in isolated aortic stenosis the left ventricle is greatly thickened and seems more likely to fibrillate during surgery. Furthermore, the enlarged and

thickened ventricle is more difficult to "pump" manually in maintaining the circulation during ventricular fibrillation and the increased muscle mass makes electrical defibrillation more difficult. When the surgeon is not prepared to proceed with dilatation of the aortic valve the presence of aortic stenosis still constitutes an absolute contraindication to mitral commissurotomy.

At the moment, the problem of aortic insufficiency is somewhat more difficult. Methods currently under development for treating this lesion surgically must await further evaluation before they can be considered satisfactory. In patients with mitral stenosis, therefore, severe aortic regurgitation which is accompanied by a wide pulse pressure and a low diastolic blood pressure should for the present be considered a contraindication to mitral commissurotomy. However, with milder grades of aortic insufficiency in which the diastolic blood pressure is not very low and the pulse pressure is not greatly widened it seems permissible to recommend surgery for the relief of functionally significant mitral stenosis. Certainly the mere presence of a basal diastolic murmur in the absence of any blood pressure changes should not contraindicate mitral commissurotomy. Under such circumstances a basal diastolic murmur may represent either an unimportant degree of aortic valvular insufficiency or else a Graham Steell murmur of relative insufficiency of the pulmonic valve. Many of the basal diastolic murmurs which are not accompanied by a widened pulse pressure disappear after successful mitral commissurotomy, indicating their probable pulmonic valvular origin. In certain patients, however, these murmurs grow louder after operation and the pulse pressure becomes significantly widened, indicating that aortic insufficiency had been present but its hemodynamic effects were "masked" prior to mitral commissurotomy.

Tricuspid Valvular Disease. Patients with mitral stenosis in whom the disease has advanced to the stage of severe "right heart failure" very frequently have signs of associated tricuspid valvular insufficiency. At times these signs will disappear with the restoration of compensation during medical treatment prior to operation. As noted in the section on classification, certain patients in this stage of the disease may not respond to medical treatment; mitral commissurotomy is usually attempted in such patients despite the increased surgical risk. When

surgery is successful the tricuspid insufficiency and severe congestive failure usually decrease and eventually disappear. Thus most patients with mitral stenosis and tricuspid involvement will be managed adequately by surgical treatment of the mitral stenosis alone.

One encounters occasional patients who retain or redevelop the signs of "right ventricular failure" and tricuspid valvular disease despite apparently successful mitral commissurotomy. In certain of these patients organic tricuspid valvular disease has been present at necropsy. Most of these had predominant tricuspid insufficiency; however, a few had significant stenosis. Thus, when severe congestive failure and signs of tricuspid valvular disease persist or develop following mitral commissurotomy, one must try to recognize those with predominant tricuspid stenosis and subject them to tricuspid commissurotomy.

In patients with signs of tricuspid valvular disease the diagnosis of predominant tricuspid stenosis may be very difficult. Preliminary work suggests that significant tricuspid stenosis may be recognized (1) when cardiac catheterization9 demonstrates a gradient in which the diastolic pressure of the right atrium exceeds that of the right ventricle, and possibly (2) when angiocardiography in the right anterior oblique or anteroposterior position shows the right atrium to remain sharply opacified in contrast to the right ventricle (analogous to the findings already described for mitral stenosis).

Pregnancy. With good medical management most patients with mitral stenosis can be brought through pregnancy safely. Under such circumstances one would certainly avoid any elective operation. However, we have encountered a certain number of pregnant patients who developed severe difficulty before the seventh month, and in whom continuation of pregnancy obviously carried a prohibitive risk. A few such patients have been subjected to mitral commissurotomy when for various reasons termination of pregnancy was not considered advisable. To date all these patients have done well and none aborted during or after the mitral commissurotomy.

Valvular Calcification. In certain patients definite calcification of the mitral valve is visible fluoroscopically. In general this is an unfavorable finding which may well have an adverse influence not only on the success of commissurotomy from a technical viewpoint but also by increasing the hazard of embolism due to calcific particles dislodged during the operation. Valvular calcification does not, however, constitute a contraindication to operation since one can never be certain preoperatively in any given patient that its presence will prove an insurmountable difficulty to the surgeon.

Subacute Bacterial Endocarditis. This disease has been quite rare among the patients evaluated for mitral commissurotomy. We have encountered only two patients with subacute bacterial endocarditis in an active phase; a few more gave a history of previous treatment for this condition. When active this disease has generally been considered a contraindication to operation. 1,2,4,5 Although experience has been limited, no difficulty has been encountered in the few patients subjected to operation after the bacterial endocarditis had been cured. The circumstances for each individual patient must govern the time permitted to elapse before surgery.

Auricular Fibrillation. The presence of this arrhythmia is not considered a contraindication to operation and the majority of patients coming to operation have permanent fibrillation. These patients do very well, provided the ventricular rate can be kept under good control by digitalization. Certain patients are encountered in whom the ventricular rate cannot be satisfactorily controlled despite extremely large doses of digitalis. In such patients one must consider the possibility of overactivity of the thyroid gland although there may be no evidence of general hypermetabolism. We have recommended that radioactive iodine be given in therapeutic doses to a number of these patients despite the fact that they appeared euthyroid; following such treatment the ventricular rate slowed with average doses of digitalis when such control was not previously possible. A rapid ventricular rate constitutes a hazard during surgery and the immediate postoperative period so that control of the ventricular rate should be achieved prior to mitral commissurotomy if at all possible.

Arterial Embolism. Previous embolism is no longer considered a contraindication to operation unless it has resulted in a severely crippled patient. On the contrary, it is now believed that repeated embolism actually constitutes an indication for mitral commissurotomy, even in the absence of significant cardiac disability. As vet, controlled statistics are not available to serve as a sound basis for this opinion. Rather, it has been based largely on the thought that removal of the left auricular appendage, together with successful opening of the stenosed mitral valve, should reduce the tendency toward formation of future thrombi. This seems to be a reasonable point of view and there is evidence that it may prove correct. In such patients, however, the surgical risk is increased due to the greater incidence of arterial embolism during surgery.

SUMMARY

Mitral commissurotomy has its place among methods currently useful in the treatment of rheumatic heart disease. The operation should be restricted to patients with significant and progressive disability due to mitral stenosis. Its use in asymptomatic patients is not justified in view of the present surgical risk.

The technical success of mitral commissurotomy depends greatly on the surgeon's experience with this procedure. Granting perfect technic, a given patient can be improved only to the degree that his cardiovascular disability is caused by simple mechanical obstruction at the mitral valve. This means that patients with disability due primarily to causes other than mitral stenosis must be recognized and excluded from operation.

With good surgery and proper medical evaluation many patients have been improved, at least on a short term basis. No one can predict with certainty the long term results or the eventual place of surgery in the treatment of mitral stenosis. It seems likely that some form of surgery will be used to relieve mechanical

mitral obstruction until the successful prevention of rheumatic fever eradicates mitral stenosis and renders such surgery obsolete. Until then, proper selection of patients will be a matter of great importance.

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Surgical Treatment of Rheumatic Heart Disease*

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THE surgical treatment of certain congenital heart lesions has been increasingly successful in the last decade. Improved methods of anesthesia and control of respiration in open chest operations together with the advent of effective antibacterial therapy are some of the factors that have contributed to the excellent results obtained in surgical correction of lesions such as patent ductus arteriosus and coarctation of the aorta. Another reason is that the operations used are not performed on the heart itself but on the large vessels within the thorax. Operations within the heart have been contemplated for a long time but trials have been only partly successful because the problems involved are of much greater magnitude than in the congenital vascular deformities.

The problem of treating patients with rheumatic heart disease is of greater importance than the treatment of congenital heart disease, for both social and economic reasons. Rheumatic heart disease is more common than congenital lesions and frequently affects individuals in their early or middle period of active life. The medical treatment of patients with rheumatic heart disease, although it may be effective in certain situations, can not abolish the basic valvular deformity and usually fails to improve the situation beyond certain limits. This limitation in medical treatment has always been obvious but agreement as to its cause has not been reached until lately. Many physicians earlier considered that the lack of improvement following the usual medical therapy was mostly due to extensive myocardial damage resulting from the rheumatic infection, and thought the mechanical imbalance of the circulation caused by the damaged valve of only minor importance. Others had the impression that the mechanical disturbance was of greater importance than damage of the myocardium in the symptoms and signs in rheumatic heart disease. As early as the turn of

the century several authors therefore proposed an operative approach to the treatment of valvular, mostly mitral stenosis.17 This eventually gave the impetus to animal studies^{1,8} but it was not until 1913 that the first patient with acquired valvular disease was operated upon. Tuffier then operated upon a young man with aortic stenosis, invaginating the wall of the aorta with the finger and dilating the aortic orifice successfully. The patient survived and was improved for several years. 75 The first successful operation for mitral stenosis was performed by Cutler in 1923. He approached the valve from the left ventricle, using a special valvulotome.22 This operation was followed by the first era of mitral surgery in which several surgeons performed operations on the mitral valve either through the left ventricle or the auricle, almost always with unsatisfactory results. 22.64a,72 Section of the valves usually caused marked mitral incompetence, giving rise to pulmonary edema and death of the patient during or shortly after the operation.24 The operation was therefore abandoned and it was not until about twenty-five years later that a renewed approach was ventured.

During the last years of this interval several surgical attempts were made to relieve the pulmonary congestion that constituted the basis for the most embarrassing symptoms in the majority of patients with rheumatic heart disease. Anastomosis between a branch of a pulmonary vein and the azygos vein, creation of an interauricular septal defect. 11,12,25 and creation of tricuspid incompetence or ligation of the inferior vena cava²⁰ were all measures aimed at relief of the overburdened pulmonary circuit. It was realized, however, that these technics were only palliative and most of them were soon abandoned as the direct approach on the mitral valve became an established procedure. 12

Following the pioneer work of Harken and his

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associates, ^{36–40} Bailey and his group^{2,3,32,63} and Smithy and his coworkers⁶⁹ in the United States and Brock in England, ^{6,7,14} surgical correction of mitral stenosis has become a widely used method of treatment with usually good, sometimes excellent results. This has encouraged several surgeons to try to devise similar methods for the relief of aortic stenosis. ^{5,53,54,62} Some have also been working on correction of mitral or aortic incompetence. ^{4,13,15,18,27,41,43,44,60,61,65,73}

All these attempts have been made in the intact, blood-filled, beating heart without the aid of vision ("digital exploration" or "palpatory surgery" according to Bailey). Several surgical groups consider that the results gained by operations performed without the aid of vision will at best be only partly successful. They are therefore working on technics that will allow operations in the heart while the blood flow is deviated through other channels. The development of artificial oxygenators that will deliver a normal blood flow to the body while the heart is being operated upon has, however, proved to be a difficult undertaking. 10,26,29,42,55,58,68,78 Such devices are more readily utilized when the demand of the body for oxygen is lessened by decreasing the body temperature. 49,50 Recent experience has demonstrated that for the purpose of intracardiac surgery this approach is feasible in man.21

Exact knowledge of both the anatomy and physiology of each valvular lesion is of utmost importance for the surgeon. His direct aim is to correct the altered structure of the valve and in this way influence the pathophysiology. The recent development of exact methods for the physiologic and roentgen-anatomic evaluation of patients with heart disease, both preoperatively and during surgical intervention, constitutes one of the fundamental reasons for the rapid evolution of heart surgery. These methods are of great practical value for the exact assessment both of the severity of a valvular lesion and of the value of a particular surgical method. In the following paragraphs the pathophysiology of the various valvular lesions will be discussed briefly in connection with the various methods of surgical treatment.

THE AORTIC VALVE

A bicuspid aortic valve is often easily attacked by a rheumatic or bacterial infection. Aortic valvular lesions may thus be present in an ordinary tricuspid or in a deformed bicuspid

aortic valve. The rheumatic infection causes a nodular valvulitis with the rheumatic nodules usually situated along the margins of the cusps, causing fibrous adhesions between them. During the acute stage thickening of the valves, irregularity of the surface and gross vascularization may also be present. In addition to the thickening, the cusps may undergo considerable shortening as a result of rolling of the free margins toward the aortic wall; in consequence, aortic incompetence will develop when the infectious phase goes over into healing. Except for this, the end-result of the healed aortic valvulitis makes for marked stenosis. The orifice is reduced to a narrow, rounded, triangular or irregular slit-like opening and the cusps are greatly deformed, adhere to each other and contain massive calcific nodules on both the aortic and ventricular surfaces.

Pathophysiology of Aortic Stenosis. Most of our knowledge of the pathophysiology of aortic stenosis has been accumulated in animal experiments or in studies on isolated heart-lung preparations.⁷⁹ It is only lately that some data have been collected regarding the circulation in aortic valvular disease in man.

Experimentally, the aortic orifice must be narrowed to between 60 and 70 per cent of its original diameter before cardiac output per beat or per minute is reduced. Nevertheless, narrowing of 15 to 30 per cent is sufficient to cause audible and recordable murmurs. The performance of the left ventricle varies according to the degree of aortic narrowing. Slight stenosis alters the ventricular pressure curve but little. In severe stenosis the intraventricular pressure curve rises to several times the normal and the systolic ascent is steeper and longer. When ventricular ejection is seriously impeded, the ventricules approach an isometric type of contraction in which the increased residual volume and marked elevation of initial tension contribute to a high systolic ventricular pressure.

The aortic pressure curve, on the other hand, shows a diminished, though prolonged, gradient of ascent after the initial period of rapid ventricular ejection. Marked vibrations in the central arterial pressure curve correspond to the aortic thrill and murmur. They indicate obstruction to, and turbulence of, systolic blood flow at the aortic orifice.

The arterial systolic pressure and the pulse pressure are typically decreased and the diastolic pressure is elevated or normal. The radial pulse

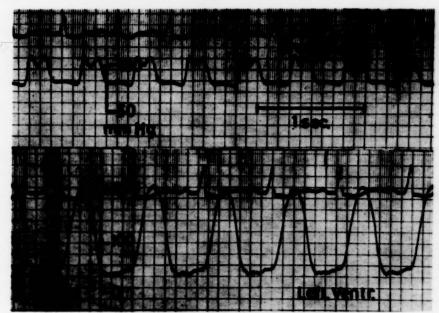


Fig. 1. Left ventricular and brachial arterial pressure curves in a case of pure rheumatic aortic stenosis, obtained by direct puncture of the left ventricle and brachial artery, respectively. Note the systolic pressure gradient ventricle-artery, the slow increase of pressure in the ventricle and the small arterial pulse pressure.

correspondingly is of the flat and delayed variety—"pulsus parvus et tardus." (Fig. 1.) These typical features of the arterial pressure pulse are modified when arterial hypertension or free aortic incompetence coexist.

The clinical symptoms of aortic stenosis are usually due to the decreased cardiac output, as a result of which the coronary flow is decreased whilst the hypertrophied left ventricular wall requires a large blood supply. This situation causes the typical angina pectoris and may contribute to the occasional fainting spells. It has been suggested that increased linear velocity of aortic blood flow causes suction past the coronary orifices and thereby myocardial ischemia. This suggestion has lately received some experimental support from studies on a circulation model.⁶⁴⁶

The increased work of the left ventricle causes marked muscular hypertrophy, detectable both in the electrocardiogram and on chest x-ray investigations.

The increased initial tension of the left ventricular muscle eventually produces an increase in the pulmonary venous pressure. This increase, however, is not marked and signs of left ventricular failure with pulmonary edema usually occur only late in the course of the disease. Once present, however, left ventricular failure reacts poorly to medical treatment and advances

rapidly via subsequent right heart failure to the fatal outcome. (Fig. 2.)

The obvious mechanical nature of the disturbance of the circulation in aortic stenosis has encouraged several surgeons to suggest different ways of relieving the stenosis. The first successful operation on a valvular lesion was, as previously mentioned, performed as early as 1913 by Tuffier who, however, never opened the heart but dilated the stenosed aortic opening with his finger, invaginating the wall of the aorta. The dramatic effect of commissurotomy in mitral stenosis has acted as a strong impetus toward new attempts in the operative treatment of aortic stenosis. Difficulties have, however, been encountered in several ways.

Glover and coworkers in 1950 tried the ventricular approach in one case but the patient died on the operating table. They then devised a new approach,³² introducing a dilating instrument through the carotid artery and were thus able to perform a successful aortic commissurotomy in three of five cases, with two deaths.³² For several reasons this method was thought to be unsatisfactory and work was continued along other lines.

Niedner in 1951 performed a successful aortic valvulotomy using the ventricular approach. He used a thin-bladed knife introduced through the wall of the left ventricle close to the septum. The

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knife was directed through the small aortic slit and the aortic commissures were cut. The patient survived and was greatly improved.⁶²

Bailey and coworkers have subsequently designed a special instrument that dilates the stenosed aortic valve so that the commissures

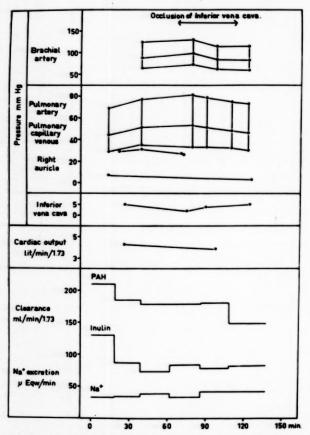


Fig. 2. Blood pressures in the systemic and pulmonary circulation, cardiac output, renal clearances and sodium excretion in a case of rheumatic aortic stenosis in chronic left and intermittent right ventricular failure. A balloon¹⁹ was inflated in the inferior vena cava below the renal veins and the reaction to ligation of the vena cava was recorded. Note the absence of any change other than the decrease in pressure immediately above the balloon. The inferior vena cava was completely occluded for sixty minutes without any subjective sensations in the patient.

more or less automatically rupture. 4.5.53.54 The instrument can be introduced either through the ventricular wall or from the aorta. In both instances a thin wire guide has to be introduced first. It has been found that the size of the opening in the diseased aortic valve may be so small and irregular that it is impossible to pass any larger instrument without the use of a guide.

Larzelere and Bailey recently reviewed the first forty-two cases of aortic stenosis—thirteen patients having isolated aortic valvular disease—

in which operation was performed using this technic. Of these thirteen, six patients had predominantly aortic stenosis but also exhibited signs of aortic incompetence. Only seven cases thus had pure stenosis. One of the thirteen patients died shortly after operation, two were markedly improved, eight improved and two were worse after the surgical procedure. The largest group operated upon were the patients with multivalvular lesions. In addition to aortic stenosis they all had varying degree of mitral involvement with stenosis or incompetence. Several patients also had slight to moderate aortic incompetence. Both aortic and mitral commissurotomy were performed at the time of operation. Of the twenty-nine patients, six died and two were unimproved, while twenty-one showed moderate to marked improvement. 53

In some patients with aortic stenosis, with or without mitral disease, dilatation of the aortic crifice has been attempted using the knife designed by Brock for correction of pulmonary stenosis. The instrument was introduced through the ventricular wall. The results have not been encouraging. In one patient (Fig. 3) mitral commissurotomy was first performed. Pressure tracings were recorded from the left ventricle and aorta before and after operation on the aortic valve. The pressure gradient from left ventricle to aorta was virtually unchanged by the dilatation. The patient, however, improved from the mitral commissurotomy. Even after the use of the Bailey-Larzelere aortic dilator, which permits a larger opening than the usual instrument, Bailey states that the postoperative valve aperture was surprisingly small.53

In rheumatic aortic stenosis the valve is always heavily calcified and cannot be considered as suitable for surgical attack as the congenitally stenosed pulmonary valve or the mitral valve. The aortic valve is also much more likely to develop incompetence than is the pulmonary valve, the blood pressure in the aorta being much higher. Consequently, the suggested operative methods have not been unanimously accepted. Studies on the movement of the diseased valves before and after attempts to operate on them may help to design better methods for surgical intervention.⁵⁶

Aortic Valve Incompetence. A minor degree of aortic incompetence is almost always present in rheumatic aortic stenosis. Sometimes the rheumatic valvulitis has caused curling and retraction of the cusps of the aortic valves, or subse-

quent ulcerous endocarditis has almost destroyed them, making incompetence the dynamically more important lesion. Aortic incompetence due to rheumatic heart disease usually is less severe than after luetic infection, which causes not only alterations of the valves but also dilatation of the aorta. Marked aortic regurgitation has a more rapidly deleterious effect on the heart than marked aortic stenosis. Left ventricular hypertrophy and dilatation apparently develop simultaneously and the heart becomes very large. With tremendous ventricular dilatation the mitral valve may become incompetent, followed by dilatation and hypertrophy of the left auricle.

Pathophysiology of Aortic Incompetence. When small aortic leaks are produced, the left ventricle empties itself more completely during the early phase of the ejection, due partly to the increased filling of the ventricle at the start of contraction and partly to the low diastolic pressure in the aorta that is easily overcome. When regurgitation is more marked this pattern is further changed. Higher systolic pressure in the aorta and ejection of large stroke volumes into it results from the increased amount of blood flowing back into the ventricle, further increasing the presystolic distention of the myocardial fibers.

In small aortic leaks the peak fall in diastolic arterial blood pressure is late and not especially pronounced. In more marked regurgitation the pressure in the aorta falls rapidly with relaxation of the left ventricular myocardium. The pressure in the arteries never drops to zero when measured exactly by intra-arterial methods.

The effective cardiac output is kept within normal limits by increasing the stroke volume with the amount regurgitated. By shortening the diastolic time this amount is kept to a minimum. The tachycardia observed [in aortic regurgitation is thus a compensatory mechanism to keep the cardiac work per stroke down. The amount of blood that may leak back in severe regurgitation has been estimated as up to 60 per cent of the stroke output.⁷⁹

The arterial systolic and pulse pressure are typically increased and the diastolic pressure low. The radial pulse is of the collapsing type—"water hammer pulse." (Fig. 4.)

In clinically manifest aortic insufficiency angina pectoris may occur, due to inadequate blood supply to the hypertrophied and dilated left ventricle, but it is less common than in

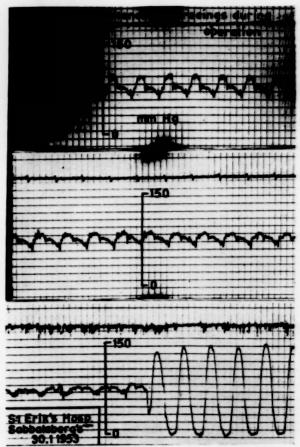


Fig. 3. Tracing obtained after commissurotomy while withdrawing a catheter from the aortic to the left ventricle in a case of rheumatic aortic stenosis and mitral stenosis. A similar tracing was again obtained after a Brock knife had been forced through the stenosed, calcified valve opening; pressure in mm. Hg.

aortic stenosis. More often the left ventricle fails, with increase in pressures in the pulmonary circuit. When signs of failure have appeared, the progress of the disease is usually rapid. It is difficult to restore compensation by medical means and another bout of failure soon follows which may not be amenable to treatment.

The location of the aortic valve, close to the ostia of the coronary arteries, precludes any direct attempt to replace the defective valves with artificial ones. Bailey has suggested introduction into the aorta of a pericardial flap that during diastole should at least partly occlude the opening and during systole be displaced by the blood stream. Operations using this technic have not been successful.¹⁵

Hufnagel has developed an artificial plastic ball valve that is placed in the descending aorta.⁴⁴ Operations in man have shown that this operation is practicable, and may result in striking

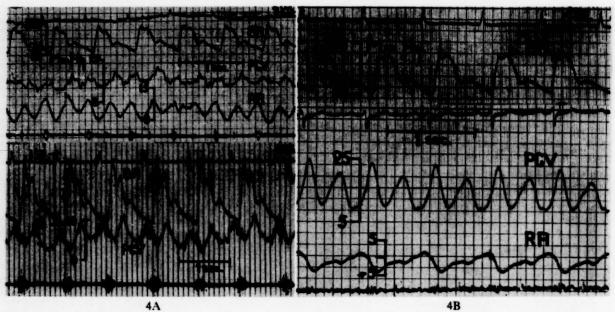


Fig. 4. A, brachial arterial, pulmonary capillary venous and right auricular pressures in patients with aortic incompetence and minimal (Case 423) and marked (Case 583) regurgitation. Both patients had normal pulmonary capillary venous pressure at rest and no signs of left ventricular failure. B, brachial arterial, pulmonary capillary venous and right auricular pressure in a patient with moderate aortic regurgitation and impending left ventricular failure. The mean pulmonary capillary venous pressure is slightly elevated at rest and the pulsations are exaggerated. This patient had luetic heart disease and the abnormal pulmonary capillary venous pressure could not be due to mitral valvular disease.

improvement in the survivors. The amount of regurgitating blood was diminished, with decreasing heart size and better function—improved total blood flow. The arterial pulse distal to the artificial valve was normalized, with unaltered pulse pressure proximal to the valve, i.e., in the coronary, cerebral and arm circulatory beds. However, the operation still carries a heavy mortality and the fate of the artificial ball valve situated in the descending aorta is as yet unknown.

The surgical treatment of both aortic stenosis and incompetence must be considered to be still in the experimental stage.

THE MITRAL VALVE

The anatomy of the mitral valve at one time interested only anatomists or pathologists. During the recent years several studies have been made by surgeons, who have had the opportunity to obtain an impression of the valve during life and compare it with anatomic specimens.

The normal mitral valve consists of two leaflets, one ventral or anterior, and one dorsal or posterior. Frequently deep notches in the margin of the leaflets occur, giving rise to an increase in the number of leaflets. 14.39 The anterior leaflet, also called the aortic, is much larger than the posterior. There seems to be little doubt that the anterior (aortic) leaflet is the main factor in effective closure of the orifice. The posterior, lesser cusps performs only a subsidiary function in sealing a narrow segment of the orifice.

Stenosis of the mitral orifice results from fusion of the leaflets at their edge and fusion and shortening of the chordae tendineae. Brock has pointed out the importance of the chordae tendineae in severe valvulitis, ¹⁴ in which not only the margins of contact of the valves adhere to each other but also the chordae tendineae become firmly adherent across the valvular opening. Even if the fused cusps are cut apart, the valve orifice still cannot open because it is held firmly by the fused and interfused chordae. They may form a firm fibrous mass which constitutes a grave obstacle to surgical alleviation of the stenosis.

When a stenosed mitral orifice is examined from the left atrium, the lesion has a characteristic funnel shape. The walls of the funnel are formed by the fused leaflets of the valve which lead down to a small opening of variable shape. This has been characterized as a "button-hole" or "fish-mouth" valve. Sometimes the valvular ring is calcified as well as the leaflets, sometimes

only the thickened leaflets are calcified. The calcium deposits may be laid down as nodules or diffusely. Not infrequently the leaflets are so adherent and rigid that almost no movement is possible. Incompetence of the valve thus usually ought to be present but in many cases no signifi-

and calcification is rare. The surgical results in patients with type II stenosis are usually poor but in type I stenosis good results may be obtained.

There is at present no method to determine the exact morphology of the mitral valve before surgery. Not until the surgeon has opened the

Table 1

HEMODYNAMIC FINDINGS IN 126 PATIENTS WITH MITRAL STENOSIS, TWENTY-ONE PATIENTS WITH AORTIC INCOMPETENCE AND TWO PATIENTS WITH AORTIC STENOSIS*

Clinical Grouping	No. of Cases	A-V O ₂ Difference	Cardiac Index (L./min./ m²BSA)	Pulse Rate	Mean Blood Pressures (mm. Hg)				
Grouping	Cases	(ml./L.)			RA	PA	PCV	BA	
			Mi	tral Stenosis			, ,		
1-11	49	39	3.65	81	1	19	13	93	
III	54	52	2.68	82	2	36	21	95	
iv	23	64	2.20	93	2 4	53	25	97	
	-		Aorta	ic Incompetence					
1-11	18	40	4.14	79	1	15	9	96	
III-IV	3	.54	3.47	86	5	36	19	89	
			Aoi	rtic Stenosis				•	
11	1	38	4.74	87	0	14	8	93	
III-IV	1	90	2.49	97	5	51	29	89	

* Grouping according to New York Heart Association.

RA = Right auricle

PA = Pulmonary artery

PCV = Pulmonary capillary venous

BA = Brachial artery

A-V O2 Diff. = Arteriovenous oxygen difference

cant regurgitation through the stenotic orifice occurs during ventricular systole, due to the fact that the ventricular opening of the funnel is pressed against the myocardium, sealing the opening in an efficient manner.

Harken and coworkers³⁹ have described two types of stenosis of the mitral valve: Type 1 is primarily a rigid, fibrous contraction of the leaflets to form a stenotic opening with little thickening or fusion of the chordae tendineae. Type II consists of an elastic funnel with marked fusion of the chordae tendineae. These fused chordae may even constitute secondary stenosis.

Calcification is common in type 1 stenosis, which occurs in about 85 per cent of all cases of mitral stenosis. Type 11 is the uncommon form

left auricle and palpated the deformed valvular apparatus can he decide whether the stenosis is suitable for surgical correction or not.

The Pathophysiology of Mitral Stenosis. It has been recognized for centuries that narrowing of the mitral orifice introduces a resistance to the flow of blood from the left auricle into the ventricle, impairing its filling and output. Early experimental work and studies on circulation models have confirmed this reasoning. Katz and Siegel, using the purse-string method to produce mitral stenosis, consistently found an immediate reduction in systolic, left ventricular and aortic pressure, with a reduction in aortic pulse pressure and a pronounced deviation in left auricular pressure. The amplitudes of the atrial

contraction wave increased markedly. The effects on pulmonary arterial and right ventricular pressures proved variable, probably depending on the status of the circulation at the time of observation. In some experiments the systolic pressure in the pulmonary artery and right ventricle decreased, and the pulse pressure in the pulmonary artery fell; in others the pulmonary arterial pulse pressure increased and with it the systolic pressure in the right ventricle and pulmonary artery. These and other results are gained in acute experiments. However, the dynamic picture obtained in the chronic, long-term experiment of mitral stenosis in man need not exhibit many features in common with the animal experiments.

Hydrodynamic studies by Allen on artificial valves in a physical system led to the conclusion that a reduction in 75 per cent of the surface area of the orifice can take place without marked increase in resistance. Similar results have been arrived at by Wiggers. Hempts to calculate the mitral orifice in man indicate similar reductions before severe symptoms occur; the methods employed are, however, too uncertain to be of real value. The severity of symptoms in man, furthermore, is due not only to the reduced size of the orifice but also, as pointed out by Brock, to a great many additional factors.

In man several studies have demonstrated that the presence of a slight degree of mitral stenosis does not alter the cardiac output or the pressures in the pulmonary circulation at rest. 280,45,52 During exercise the pulmonary capillary-venous and arterial blood pressures increase with the increasing output, which may be sufficient for rather large demands.

With more marked narrowing of the mitral orifice the pressures in the pulmonary circuit tend to become higher and the cardiac output lower. During exercise the output may or may not be sufficient for the need of oxygen in the tissues, but the pulmonary vascular pressures increase, sometimes to the level of impending pulmonary edema.

With tight mitral stenosis the cardiac output is low and the pulmonary capillary-venous and pulmonary arterial pressures are high. The response to exercise is characterized by marked increase in blood pressures in the pulmonary circuit, with little or no change in cardiac output. When the right ventricle finally proves inadequate to the increased work against the pulmonary arterial pressure, the pressure in the

right auricle increases and the clinical picture of right heart failure appears. (Table 1.)

This general description of the dynamic behavior of the circulation in patients with mitral stenosis is modified by the extent of mitral incompetence and its effect on the left ventricle, the degree of pulmonary vascular disease, the extent of myocardial damage, the reaction of the kidneys and other organs, and by numerous other factors.

Surgical Treatment. Harken and his associates have designed the surgical technic known as valvuloplasty. 30,36,37,38,39,40 Bailey and coworkers developed the technic for operation on the stenosed mitral valve that is known as commissurotomy.2,32 Common to both types of operation, and essential to their successful performance, is the use of the left auricular appendage as the avenue of approach. The essential difference between Bailey's and Harken's technics consists in their attitude toward the use of a knife-like instrument for cutting the stenosis open. Harken principally prefers to use the index finger to rupture the fused commissures of the mitral valve and resorts to some sort of instrument only when this is difficult or impossible, as in type II mitral stenosis. Bailey, on the contrary, prefers to use a valvulotome and has found that the best use of the knife is to make several small cuts through the adhesions along the commissure until an incision of satisfactory length has been accomplished. Both authors cite several reasons to support their ideas about the proper technic. The results in large series from both groups have been similar and the differences in technic may be more apparent than real.^{2,40,48} We prefer using the finger fracture technic, first dilating the anterior commissure and only infrequently resort to a valvulotome.

Selection of Patients and Results. When the recent era of mitral surgery started, patients with severe symptoms and advanced lesions were, for the most part, operated upon. As soon as experience showed that it was possible to make a satisfactory opening of the stenosed mitral valve without a high mortality, the indications were extended to patients with less advanced disease. It was soon found that the mortality rate in connection with the operation showed significant correlation with the severity of the disease, milder degrees of the heart lesion having a lower mortality. This has caused many

to include even moderate or mild cases among those to be recommended to surgery.

As for the criteria for selection of suitable patients for operation, most groups now use about the same indications. 2.6,7,12,16,28a,31,32,33,35,40,45,46,48, 63,67,71,74,77,81 Differences of opinion as to when to operate and when not to operate are rather small. The patients are usually classified more or less according to the severity of symptoms and signs-sometimes including the findings at catheterization of the heart-and operation is advised in all except those with little symptoms or with complicating diseases. Some try to decide before operation whether the mitral valve is amenable to successful operation or not, and attempt to assess the state of the valve also. 67 Most surgeons, however, do not think it possible to predict the condition of the valve until the auricle is opened and the valve is accessible to palpation. 14

A classification of patients with mitral stenosis as to suitability for operation has been proposed by several surgeons, differing in the terms used rather than in principles. Group 1 comprises the benign or asymptomatic cases, Group 2 the statically handicapped, Group 3 those with progressive symptoms and Group 4 those in the terminal stages of disease. This grouping should not be confused with the one advocated by the New York Heart Association, as there is a considerable difference in principles although some overlapping occurs between the groups of the two different systems.

The patients belonging to Group 1 have the characteristic physical signs of mitral stenosis but exhibit no symptoms. In the Stockholm experience this type of patient is not uncommon. (Table 1.) Hemodynamically, the patients in this group are characterized by normal blood flow and normal pressures in the pulmonary circuit at rest, except for a small presystolic pressure rise in the pulmonary capillary venous pressure curve.52 It should be pointed out that a patient may remain in this group throughout life. The disease is by no means always progressive and many patients reach old age without untoward symptoms. It is generally agreed that patients belonging to this group should not be operated upon. This group corresponds roughly to Classes 1 and 11 of the New York Heart Association.

The patients classified as statically incapacitated, Group 2, usually are on the borderline between the New York Heart Association's

Classes II and III. They reach a level of dyspnea and fatigue on effort which is not disabling, and remain at this level. During the first years of mitral surgery most surgeons did not want to operate upon patients in this group but with increased experience many now advocate surgical treatment for these patients. The rationale for operation is prevention of progression of the disease. The operative mortality rate in this group is very low, which makes the operation still more attractive for the surgeon. It is, however, unlikely that surgical intervention prevents all progression of the disease and many of these stationary cases do not progress anyhow. It therefore seems a better policy to follow patients in this group carefully and frequently and to refer them for operation as soon as they show signs of a downhill course.

Patients who slowly deteriorate despite appropriate medical therapy belong to Group 3. Dyspnea, orthopnea, cough and ease of fatigability increase, and the patients begin to experience difficulties as soon as they exert themselves. They then correspond to the definition used for Class III of New York Heart Association. Hemodynamically, the pressures in the pulmonary circuit are markedly elevated and the cardiac output tends to be low. The progressive character of the disability constitutes a definite indication for surgery. The life expectancy for these patients is uncertain and operation should be performed as soon as the progressive pattern becomes clear. The patient most appropriate for surgical intervention has had episodes of pulmonary edema or gross hemoptyses or both, and has a relatively normal-sized heart. The right ventricle easily transports blood into the lungs even during the increased demands of exercise but the blood cannot be removed through the stenotic mitral orifice with the same ease.

The patients that are in the terminal stages of disease are placed in Group 4. They have severe symptoms even at rest (Class IV, New York Heart Association) and have usually been or are in right heart failure. The heart is grossly enlarged. The risk of operation in these patients is great and the operative mortality rate has ranged between 20 and 40 per cent. On the other hand, some patients may have marked benefit from valvulotomy and the opinion has been expressed that no patient should be denied surgery because the disease has progressed too far. It is the

responsibility of physicians to send patients to operation before they reach this stage.

It is thus generally agreed that the most suitable candidates for surgical treatment are those with marked mitral stenosis, with little or no evident regurgitation, and with manifest

TABLE II
HEMODYNAMIC FINDINGS BEFORE AND AFTER
COMMISSUROTOMY*

State	A-V O ₂ Difference	Cardiac Index	Pulse Rate	Mean Blood Pressures (mm. Hg)				
	(ml./L.)			RAţ	PA	PCV	BA	
I Danamana sina	45	3.0	89	-	45	25	00	
Preoperative			-	2			90	
Postoperative II	36	3.9	92	1	25	12	92	
Preoperative	43	3.2	74	2	27	19	85	
Postoperative	46	3.0	85	1	25	17	90	

^{*}Series includes nineteen patients with marked postoperative improvement (i) and eleven patients with slight or no improvement after the operation (ii). The postoperative studies were performed about six weeks after the operation. The patients in the improved group have shown continued clinical improvement up to three years after the operation.

† Symbols as in Table 1.

signs and symptoms of pulmonary congestion exertional or paroxysmal dyspnea, cough, pulmonary edema or hemoptysis. The smaller the heart, the better the outlook. Those with large hearts and chronic congestive failure are poor risks and are unlikely to benefit significantly from surgery. Auricular fibrillation or previous embolism increases the hazard slightly but are no contraindication per se. On the contrary, some consider arterial embolism to be a definite indication for surgery, as the risk for subsequent emboli is less after operation. It is unlikely, except in special instances, that substantial benefit can be gained for patients beyond fifty years of age. Dexter and his associates have, however, seen several patients beyond the age of sixty28b and Janton, Glover and O'Neill report successful surgery in thirty-five patients between fifty and sixty years of age with only 8.5 per cent mortality.47

Contraindications to surgery are few: subacute bacterial endocarditis and intractable congestive heart failure. Most authorities also consider rheumatic activity a contraindication but Dexter states that activity is more easily coped with if the stenosis is relieved. 286 It is also difficult to define what is meant by rheumatic activity in view of the high frequency of Aschoff nodules in atrial biopsies taken at operation in patients

who were considered on routine clinical and laboratory studies to be free of rheumatic activity. 9.57

The diagnosis of complicating valvular lesions is not always as easy as it ought to be, especially in patients with severe symptoms and marked enlargement of the heart. 34,51 Some patients with marked mitral incompetence or disabling aortic stenosis have therefore been operated upon, without any improvement. Mild degrees of involvement of other valves is of little importance as long as the stenosed mitral valve is mainly responsible for the patient's disability.

Mitral commissurotomy is now a routine procedure. Reports of the results of operation have been published from a great many centers. Most of the reports are concerned only with a clinical follow-up study but some also contain postoperative hemodynamic studies. All reports demonstrate the marked improvement obtained in the majority of patients, whether the opinion is based on clinical impression or exact hemodynamic studies. There is, of course, some difference in the exact percentage of patients improved but all reports indicate that about 60-70 per cent of operated patients are improved and many include some patients in whom improvement has been striking, life-saving or otherwise spectacular. Long-term follow-up studies are largely lacking but the largest series of cases followed for the longest time indicates that benefit from the operation may last for more than five years in the majority of patients.

The mortality rate differs greatly in different patient groups, being only 3 per cent in Group 2, 10 per cent in group 3 and 30 per cent in Group 4 patients.³¹ The lowest mortality rates have been attained by those surgeons who have operated upon the largest number of patients.

Table II shows the results of hemodynamic studies before and after valvuloplasty in a Stockholm series. Sixty per cent were considered improved, some patients markedly so. In these patients subjective improvement has lasted up to three years.

The general consensus thus is that patients with pure mitral stenosis without right heart failure or bacterial endocarditis and with progressing symptoms should be operated upon. No patient should be denied operation because of the severity of the disease, as long as it is not complicated by other valvular lesions of hemodynamic importance.

There are several sequelae of the rheumatic

inflammation of the leaflets and chordae tendineae that may give rise to *incompetence of the mitral valve*: rigidity of the margins preventing the closure of the valve; shortening of one or both cusps so that they cannot meet; rupture of chordae, or shortening of the chordae tendineae with increasing or decreasing mobility of the leaflets; and, finally, dilatation of the atrioventricular ring are some anatomic features that contribute to incompetence of the valve.

Brock has described three forms of mitral incompetence: (1) A small regurgitant stream occurring from a small, grossly stenosed orifice. In this case the stenosis is the main disability and the incompetence may be corrected when the valve is freed. (2) A moderately large regurgitant stream occurring from a narrow but not grossly stenosed orifice. This type is common and represents the most severe grades of damage to the valve by rheumatic infection. (3) A powerful current of blood escapes through a large orifice in ventricular systole. No stenosis is present. This form is due to the additive effect of marked dilatation of the mitral ring superimposed upon damage on the leaflets or rheumatic infection.

Mitral incompetence causes a regurgitation of blood into the auricle during left ventricular contraction. Instead of the normal fall in left atrial pressure in early systole, due to left ventricular emptying and the downward movement of the atrioventricular ring, there is a rise of pressure in the left atrium that propagates through the veins back into the pulmonary capillaries, with paradoxic fluoroscopic pulsation of the left atrium and a corresponding wave in the electrokymogram. The compensatory mechanisms that come into play in the sudden creation of a mitral leak were studied by Wiggers and Feil in 1922 by recording pressure pulses in the left atrium and ventricle. They showed that the major elevation of left atrial pressure and the regurgitation occur simultaneously with discharge of blood into the aorta. They also demonstrated that the volume of regurgitation is conditioned not only by the size of the leak and the mean pressure in the ventricle, but also by the velocity of tension development during isometric contraction. Thus more blood regurgitates when ventricular contractions become hypodynamic. 79

Mitral insufficiency, therefore, is dangerous not only by virtue of the circulatory changes induced as a result of the valvular deficiency but also because of the constant vulnerability to decompensation from any cause which weakens ventricular contraction.

Experimentally, 50 per cent of the left ventricular stroke volume may be regurgitant into the left atrium, yet allow a normal left ventricular output. In dogs, experimental acute mitral insufficiency causes a rise in the left atrial pressure and slight increases in right ventricular and pulmonary arterial pressures, but no change in cardiac output or arterial pressure and no cardiac decompensation.

With the discharge of blood in two directions, mitral regurgitation results in increased work for both ventricles to maintain a normal blood flow. Since resistance is not increased the strain on the left ventricle is less than in arterial hypertension or aortic stenosis. Heart failure is uncommon if mitral stenosis is not also present and is usually precipitated by active myocarditis.

Mitral incompetence may occur as a symptomless disease, with only slight enlargement of the left ventricle, an apical systolic murmur and normal pulmonary circulation at rest and during moderate exercise. (Fig. 5A.) When this slight degree of incompetence is combined with stenosis the hemodynamic sequelae of the latter lesion dominate the picture. This corresponds to the first anatomic form described by Brock.¹⁴

In free regurgitation, corresponding to the third form, the heart is markedly enlarged, the pulmonary arterial and pulmonary capillary venous pressure are moderately increased and the effective cardiac output is normal. (Fig. 5B.) Even with marked enlargement of the heart the symptoms at rest are slight but increase sharply with exercise. When left ventricular failure supervenes, which may occur late in the course of the disease, the output decreases and the pressures in the pulmonary circuit increase further.

Gorlin and coworkers studied the pulmonary circulation in eleven patients with combined stenosis and incompetence of the mitral valve and one patient with pure mitral insufficiency. They concluded that mitral incompetence in the absence of co-existent stenosis or left ventricular failure is characterized by fatigability instead of by dyspnea, frequent absence of hepatomegaly and edema, an apical systolic murmur, auricular fibrillation, an invariably enlarged left atrium by fluoroscopy (often with paradoxic pulsation) and, not uncommonly, absence of any ventricular preponderance by

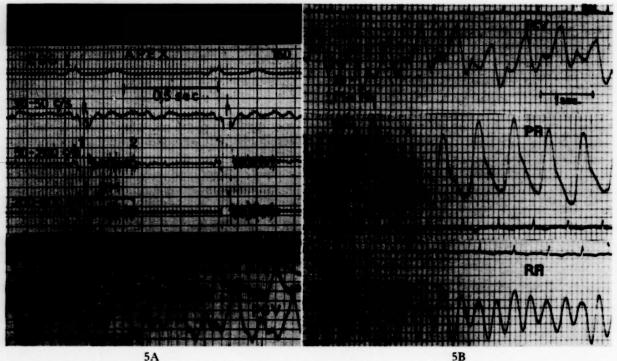


Fig. 5. A, phonocardiogram, brachial arterial and pulmonary capillary venous pressure in a patient with mitral incompetence without any incapacitating symptoms. The pulmonary capillary venous pressure shows a marked V-wave but is otherwise normal. B, pulmonary arterial, capillary venous and right auricular pressure in a patient with rheumatic mitral incompetence with progressive pulmonary symptoms. Note the high V-wave and high mean pressure of the pulmonary capillary venous pressure. Cardiac output was normal at rest but failed to increase during exercise.

electrocardiogram. When left ventricular hypertrophy was present, it usually indicated severe regurgitation.

In the presence of mitral stenosis, incompetence can be suspected from a history of more fatigue and less dyspnea, absence of major congestive phenomena, the presence of a pulsating left atrium, and the type of ventricular hypertrophy by electrocardiogram.³⁴

Surgical correction of a leaking valve is much more difficult than the opening of a stenosed valve orifice and less satisfactory results have been obtained in the attempts to correct an incompetent mitral valve. As early as in 1938 Murray reported partial correction of experimentally created mitral incompetence by means of transventricularly positioned autogenous free vein grafts. This method was used in a few patients. 60 Bailey and associates have described an adaptation of this method, using a pericardial pedicle instead of vein grafts. These grafts thus act as flap-valves, preventing most of the regurgitation. Bailey and his colleagues have had some successful cases with this method but others do not consider it sound. 15 Plastic valves have been suggested by Denton and Harken but the

results of their use in patients have not been encouraging. 27.41

Of all the methods suggested and in some cases attempted in the surgical treatment of the various valvular lesions caused by rheumatic fever, other infectious diseases or of congenital origin, only the valvulotomies for mitral stenosis and pulmonary stenosis, respectively, have given results that have established them as suitable for use in the practical work of treating patients. They are also the only operations that do not carry an undue mortality rate and are technically easy enough to be recommended for general use.

The feverish activity that now characterizes the field of research in pump-oxygenator mechanisms for extracorporeal circulation promises results that may be transferred to the operating room. 10.21.26.23.42.55.58.68.78 As soon as it is possible to operate in the heart, when the blood is propagated by some other mechanism, and the bloodless heart is open to inspection, even for a short period, reconstruction of damaged valves will be carried out by technics completely different from those now suggested. This time is perhaps not far off. It is possible that success will be attained more easily if the metabolic demands

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of the body simultaneously can be diminished by hypothermia. 49,50 With the use of extracorporeal oxygenation and circulation, perhaps combined with hypothermia, heart surgery will enter a new era and operative methods now impossible to conceive will add to the possibilities of treatment in patients with rheumatic heart disease.

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Clinical and Laboratory Manifestations of the Postcommissurotomy Syndrome*

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widely accepted procedure for the alleviation of mitral stenosis of rheumatic origin. 1-6 One of the more frequent and puzzling complications of this operation, the "postcommissurotomy syndrome," 7-18 has not received the attention it deserves, and is the subject of this report.

The postcommissurotomy syndrome is characterized clinically by chest pain, fever and cough, often with signs of pleuritis and pericarditis. It has appeared as early as ten days after operation and has recurred as late as fourteen months postoperatively. It incidence varied from 10 to 30 per cent in different reports. 7,9,11,12 It does not appear to be due to acute rheumatic fever, bacterial infection, pulmonary infarction or the direct trauma of surgery alone. A similar complication has not been observed following cardiac or thoracic surgical procedures in non-rheumatic patients.

In the present report the clinical and laboratory manifestations of the postcommissurotomy syndrome are analyzed in order to delineate the syndrome more adequately and, if possible, to determine the factors responsible for it.

MATERIALS AND METHODS

The sixteen patients comprising this study were selected from the Medical and Surgical Services of The Mount Sinai Hospital. They ranged in age from twenty-one to forty-six years. Eleven were women and five were men; thirteen were white and three were Negro. In each patient the indication for mitral commissurotomy was hemodynamically significant mitral stenosis with myocardial insufficiency of varying degree. In addition to mitral stenosis, two patients had associated mitral insufficiency

and three had probable mild aortic insufficiency. All patients were carefully selected so that none was operated upon who had overt acute rheumatic fever or suspicion of even moderate rheumatic activity.

In addition to the clinical examination, preoperative evaluation included appropriate roentgenographic, electrocardiographic and cardiac catheterization studies. Urine examination, complete blood count, erythrocyte sedimentation rate (Westergren), antistreptolysin-O¹⁴ and C-reactive protein determinations were made in each instance.

At operation the pericardium was opened, the left auricular appendage amputated and a finger-fracture commissurotomy accomplished through the atrial orifice. The auricular stump was closed with silk sutures; the pericardium was loosely closed with interrupted silk sutures, allowing for free drainage between the pericardial sac and the left pleural space. Postoperatively penicillin alone or with dihydrostreptomycin was administered. The patients were observed postoperatively in the hospital for periods varying from thirteen to eighty-five days. After discharge from the hospital follow-up examinations were carried out at intervals varying from semi-weekly to as infrequently as once in four months. The shortest follow-up reported is two weeks, the longest fifteen months. The patients were instructed to report any symptoms suggestive of the postcommissurotomy syndrome. If the syndrome whether severe or mild, developed the patients were hospitalized, and they were then observed closely in the Adult Rheumatic Cardiac Clinic of The Mount Sinai Hospital. During episodes of

§ The operative procedures were performed by Drs. M. M. Ravitch, A. Himmelstein, L. Blum and R. Nabatoff.

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the postcommissurotomy syndrome our studies included white blood count, erythrocyte sedimentation rate, antistreptolysin-O determinations, blood cultures, nasopharyngeal cultures, chest x-rays and electrocardiograms.

The C-reactive protein (CRP) determination was a point of special interest in this study. Postoperatively, samples of blood for this determination were taken daily for one week, thereafter three times weekly during the remainder of the hospital stay, and at each Clinic visit following discharge from the hospital. During episodes of the postcommissurotomy syndrome samples of blood were taken daily in many instances, although in some patients only sporadic blood samples were available. The blood was analyzed for the presence of C-reactive protein according to the method of Anderson and McCarty;15 1.5 cm. of antiserum to C-reactive protein and an equal amount of the patient's serum were drawn into a capillary tube (0.7 to 1.0 mm. outside diameter), the tube was incubated at 37°c. for two hours and then refrigerated at 4°c. overnight. When no visible precipitate was present, the test was considered negative. Each millimeter of precipitate was considered 1 plus; the maximum precipitation was designated 8 plus.

RESULTS

Incidence and Duration. Sixteen patients have been followed up for periods from two weeks to fifteen months after commissurotomy. (Table 1.) Ten of the sixteen patients developed the postcommissurotomy syndrome, of whom seven had multiple attacks. (Table II.) In all, twentytwo episodes occurred. One patient had four attacks, the last occurring seven months following the operative procedure. Fourteen of the twenty-two attacks occurred within two months following surgery; five were delayed as long as four to seven months. (Table III.) Twelve of the attacks lasted less than a week, seven lasted one to two weeks and three were prolonged up to three weeks. All patients recovered from the illness without any known sequelae.

Symptoms (Table IV). The onset of the postcommissurotomy syndrome was usually abrupt and was signaled by the appearance of chest pain. In all but three instances the patient was afebrile and asymptomatic preceding onset of the illness; in the three exceptions the postcommissurotomy syndrome was continuous with the immediate postoperative period. The appearance of this syndrome was not related to the occurrence of postoperative pericardial friction rubs, which were noted in eight instances. Of these latter, only four developed the postcommissurotomy syndrome. Nor did the development of left hemothorax or postoperative

TABLE 1
POSTOPERATIVE FOLLOW-UP OF SIXTEEN PATIENTS AFTER

MITRAL COMP	HISSURUT OM I
No. of Months	No. of Patient
0-1	2
1-3	3
4-6	3
7-12	5
12-15	3

TABLE !

IABL	E II
RECURRENCES OF POSTCOM	MISSUROTOMY SYNDROME
No. of Attacks	No. of Patients
1	3
2	3

TABLE III

ONSET OF POSTCOMMISSUROTOMY SYNDROME AFTER SURGERY

MSE I OF FOSTCOMMISSEROI	OMI SINDROME ATTER SCI
No. of Months	No. of Patients
0-1	7
1-2	7
2-4	3
4-7	5

TABLE IV

SYMPTOMS OF POSTCOMMISSUROTOMY SYNDROME

Symptom N	o. of Episodes
Pain:	•
Left chest pain 14	
Right chest pain 4	
Bilateral chest pain 4	
Aggravation by respiration 13	
Radiation to shoulder 7	
Radiation to elbow 1	
Fever	21
Cough	
Hemoptysis	
Dyspnea	
Arthralgias	
Myalgias	

incisural pain predispose to the postcommissurotomy syndrome.

The pain was described most commonly as sharp, stinging, cutting or knife-like. It was usually present on the left side but was occassionally right-sided or bilateral. Radiation to the left shoulder was not infrequent. In most instances the pain was aggravated by respiration, cough or twisting of the trunk and evoked a sense of shortness of breath limiting respiratory excursion. In two cases the pain was maximal substernally with radiation to the left anterior

chest. In both instances swallowing aggravated the pain and relief was afforded when the patient assumed the upright position and leaned forward. In most patients the pain persisted without interruption for hours or days and recurred throughout the period of the illness. Most effec-

TABLE V
PHYSICAL SIGNS OF POSTCOMMISSUROTOMY SYNDROME
FOURTEEN EPISODES IN NINE PATIENTS
Physical Sign
No. of Episode

FOURTEEN EPISODES IN NINE PATIENTS	
Physical Sign No. of	Episode
Lungs:	
Rales	. 12
Left lung 8	
Right lung 1	
Bilateral	
Pleural effusions	. 13
Left	
Bilateral 2	
Pleural friction rubs	. 5
Left 4	
Right 1	
Heart:	. 4
Paroxysmal auricular fibrillation 1	
Pericardial friction rub 1	
Pericardial effusion 2	
Arthritis	. 1

tive relief was afforded by salicylates. In some patients morphine or demerol® was required.

In twenty-one instances fever was noted coincident with the onset of pain. Daily spiking levels of 102° and 104°F. often occurred, with sweating and flushing. Chills and chilliness were usually absent. The fever usually remitted with subsidence of the pain.

Other symptoms were secondary in importance to the pain and fever. Cough, dyspnea and hemoptysis occurred in only four instances. In such cases cough persisted for days and was non-productive. Dyspnea was usually attributable to the diminished respiration secondary to the chest pain. Diuretic therapy failed to modify the cough and dyspnea, which subsided with disappearance of the chest pain. There was, however, one instance of frank pulmonary congestion associated with paroxysmal auricular fibrillation requiring vigorous measures for control of the congestive heart failure. When hemoptysis appeared, it lasted less than twentyfour hours. All patients with hemoptysis during the postcommissurotomy syndrome had experienced this symptom prominently before commissurotomy.

Migratory arthralgias occurred in four patients and were associated with myalgias of the arms and legs, persisting only one or two days, in two cases. There were no untoward psychologic reactions in any patients; in a few who were ill for a prolonged time, mild mental depression appeared.

Physical Signs (Table v). Despite the high fever and severe chest pain, none of these patients appeared critically ill. The most striking

TABLE VI LABORATORY DATA OF POSTGOMMISSUROTOMY SYNDROME

Laboratory Test	No. of Episodes Studied	No. of Episodes with Abnor- mal Test
Leukocytosis	12	7
Rapid erythrocyte sedimentation		
rate	12	9
Elevated antistreptolysin-O	8	1
Positive CRP	16	14
Electrocardiographic changes	12	2
Chest x-rays:	14	
Left pleural effusion		9
Bilateral pleural effusions		2
Pericardial effusion		2
Bacteriologic studies:		
Blood culture	6	0
Pleural fluid cultures	2	0

findings on examination were in the lungs. Rales, mostly left-sided, were usually inspiratory, medium, moist and "sticky"; they were located in the lower half of the lung posteriorly, extending into the axillas. Alterations of breath sounds were frequently present but no discrete pattern was noted. Pleural effusions occurred, persisted for days or weeks and often remained long after remission of the clinical symptomatology. Reabsorption of the pleural effusions was spontaneous in most cases but thoracentesis was necessary on several occasions. In general, the cardiac findings were meager. Tachycardia was common, either regular sinus tachycardia or, if the basic rhythm was auricular fibrillation, an irregular but rapid ventricular response. In one instance paroxysmal auricular fibrillation appeared but could be readily controlled with digitalis and disappeared within three days. Pericardial effusions were detected by physical signs in two patients; in one of them a pericardial friction rub was noted, which recurred intermittently for several weeks following remission of the pain and fever but did not develop into cardiac tamponade, hence pericardial tap was

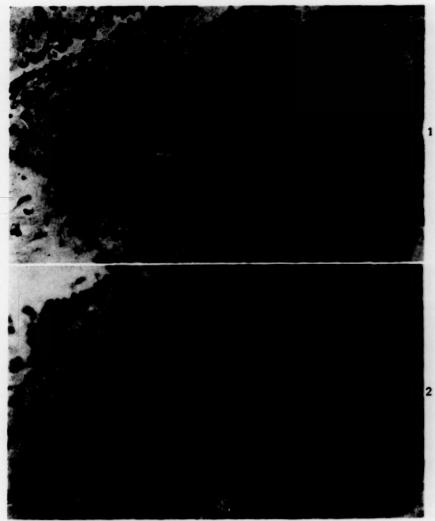


Fig. 1. Aschoff bodies in left auricular myocardium, demonstrating typical cellular morphology.

Fig. 2. Aschoff body in left auricular myocardium, demonstrating fibrinoid changes of connective tissue.

not attempted. The heart sounds were of normal or slightly diminished intensity, there were no changes in the character of the cardiac murmurs, and gallop rhythm was absent.

In one case moderate swelling and tenderness of the wrist was observed on the first day of the postcommissurotomy syndrome, subsiding within twelve hours following institution of salicylate therapy. No other evidence of arthritis was encountered. Skin eruptions and subcutaneous nodules were not present.

Laboratory Data (Table VI). Anemia was uniformly absent. The white blood count was elevated in seven of twelve patients, in four of whom levels between 13,000 and 16,000 were noted. The sedimentation rate was elevated in nine cases, markedly in seven. Electrocardio-

graphic studies revealed paroxysmal auricular fibrillation in one case. In another case progressive S-T segment and T wave changes indicative of acute pericarditis were noted. In the remainder only minor and non-progressive T wave alterations of a non-specific nature were observed. Radiographic studies of the chest were carried out in fourteen instances of the postcommissurotomy syndrome but characteristic pericardial effusion was found only twice. No well defined changes in cardiac size and shape were observed in the remaining cases. Pleural effusions were noted in eleven instances. Pulmonary infiltrations were absent; no findings consistent with pneumonia or pulmonary infarction were seen.

Pleural fluid obtained from two patients

showed the characteristics of an exudate. In one, lymphocytes were predominant, and in the other, eosinophils. Bacteriologic cultures of blood and pleural fluid were sterile.

Data Pertaining to "Rheumatic Activity." Fifteen of the patients in this series had auricular

TABLE VII

RELATION, OF POSTCOMMISSUROTOMY SYNDROME TO THE PRESENCE OF ASCHOFF BODIES IN AURICULAR BIOPSIES AND TO PREOPERATIVE C-REACTIVE PROTEIN AND ANTISTREPTOLYSIN-O DETERMINATIONS

	No.	Positive Biopsy	Ele- vated Pre- oper- ative CRP	Elevated Pre- opera- tive Anti- streptoly- sin-O
Patients with post- commissurotomy syndrome	9	5	3	4
Patients without post- commissurotomy syndrome	6	4	1	1

biopsies performed at the time of surgery. Careful examination of these appendages for Aschoff bodies, inflammatory reaction, fibrosis and muscular changes was made. The "Aschoff body," the characteristic lesion of rheumatic activity, is defined 16 as containing "evidences of disorganization in the fibrous tissue in which it occurs, the collagenous fibers showing swelling, eosinophilia, granular degeneration or necrosis. The degenerative change is accompanied by a rather special sort of inflammatory infiltrate in which large, irregular cells with ragged edges, basophilic cytoplasm and one or more vesicular nuclei with "owl-eyed" nucleoli are present. In addition, various other less characteristic inflammatory cells may be present, for instance, lymphocytes, plasma cells and histiocytes." Such lesions (Figs. 1 and 2) occurred in five of nine patients who developed the postcommissurotomy syndrome. Of the six patients who did not develop the postcommissurotomy syndrome, four had biopsies containing "Aschoff bodies." (Table vii.) Thus the presence of pathologic stigmata of rheumatic activity, as represented by Aschoff bodies in the auricular appendages, bore no relation to the development of the postcommissurotomy syndrome.

The presence preoperatively of C-reactive protein in the patient's blood or of an elevated

antistreptolysin-O test did not correlate with the subsequent appearance of the postcommissurotomy syndrome. The preoperative C-reactive protein determination was positive in three of nine patients who developed the postcommissurotomy syndrome, as compared to one positive in six patients who remained well. Four patients of nine who later developed the postcommissurotomy syndrome had elevated preoperative antistreptolysin-O values whereas only one of the remaining six was elevated. Conclusions are not warranted because of the small numbers involved, but these findings would suggest that no positive correlation exists between these tests and occurrence of the postcommissurotomy syndrome.

Antistreptolysin-O determinations were performed in eight episodes of the postcommissurotomy syndrome. Of these only one showed serial elevations significantly greater than the preoperative level. The other cases demonstrated no significant changes during the illness.

The most constant and most sensitive laboratory index of the postcommissurotomy syndrome was the appearance of C-reactive protein in the serum. This abnormal protein was demonstrated in fourteen of sixteen episodes. Of the remaining two, in one case only a single determination was made, on the second day of the illness when the patient was receiving salicylates. In the second instance the C-reactive protein was absent from a single blood specimen obtained on the fourth day of the illness while the patient was asymptomatic. In all other cases studied the C-reactive protein was an accurate indicator of the presence of the postcommissurotomy syndrome.

The C-reactive protein appeared in the blood within twenty-four hours after the onset of clinical manifestations. Blood was obtained in eight cases within seventy-two hours; in the remaining six it was not available for one to two weeks. Variations in the level of the C-reactive protein often mirrored the clinical fluctuations of pain and fever (see case reports); however, the maximum level of C-reactive protein in the blood (Table VIII) was not a good index of the severity of the illness. Changes of the level generally were useful in predicting the decline of pain, fever and physical signs but occasionally the C-reactive protein was found to persist in the blood of patients for a variable period following remission of fever and pain. In one case it persisted four weeks. (Table 1x.) Changes of the level of the C-reactive protein occurred quickly and

more accurately reflected the changing clinical state than did the erythrocyte sedimentation rate and the white blood count. The erythrocyte sedimentation rate often remained elevated for months following disappearance of the postcommissurotomy syndrome, long after the C-re-

TABLE VIII
MAXIMUM TITER OF C-REACTIVE PROTEIN DURING
POSTCOMMISSUROTOMY SYNDROME

						-	Γ	it	e	r								N	V	0	of	Patients
0		4	4																			2
Low																						
Mod																						
High																						

TABLE IX

PERSISTENCE OF C-REACTIVE PROTEIN FOLLOWING ONSET OF
POSTCOMMISSUROTOMY SYNDROME

Days	No. of Patients
8-14	4
15-21	5
22-48	4

TABLE X

ANTIBIOTIC PROPHYLAXIS OF THE POSTCOMMISSUROTOMY SYNDROME

	No.	With Prophy- laxis	Without Prophy- laxis
Episodes of postcommis- surotomy syndrome	22	11	11
Patients without postcom- missurotomy syndrome	6	4	2

active protein was absent from the patient's blood. The application of the C-reactive protein determination for aid in diagnosis and management of the postcommissurotomy syndrome is illustrated in the appended case reports.

Chemoprophylaxis. Antibiotic prophylaxis was instituted in many cases postoperatively in order to determine whether development of the postcommissurotomy syndrome could thereby be prevented. Upon discharge from the hospital many patients were instructed to take oral buffered penicillin K tablets in doses of 200,000 units daily, and this was continued for six months postoperatively. One patient received gantrisin, 1.0 gm. daily. As shown in Table x, chemoprophylaxis did not seem to modify the development of the postcommissurotomy syndrome. There was no apparent difference in the character, intensity or duration of the illness whether or not penicillin was received prior to its onset.

Aspirin in doses of 2.4 gm. daily was administered for periods of four weeks to six months postoperatively to five patients. In some instances salicylates were given after a first episode of the postcommissurotomy syndrome. No untoward effects resulted. In four patients signs

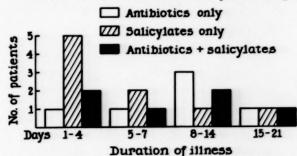


Fig. 3. Treatment and duration of postcommissurotomy syndrome.

and symptoms of the postcommissurotomy syndrome failed to appear. One patient (E. C.) had a typical episode of the postcommissurotomy syndrome one month after institution of aspirin therapy, but increase of the dose of aspirin from 2.4 to 3.6 gm. daily resulted in rapid subsidence of the symptomatology.

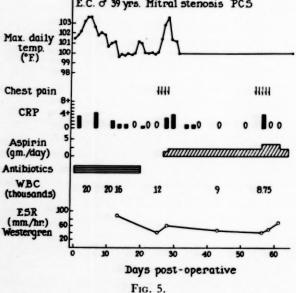
These preliminary observations concerning the effects of aspirin are sufficiently encouraging to warrant the recommendation that it be used more widely for suppression of the postcommissurotomy syndrome.

Treatment. Evaluation of therapeutic measures in the postcommissurotomy syndrome is difficult because of the variability in duration of each episode. Treatment was given in twentyone of the twenty-two episodes of the postcommissurotomy syndrome. Figure 3 records the relation between treatment and the duration of the postcommissurotomy syndrome. In six instances antibiotics only were administered; penicillin, streptomycin, aureomycin, terramycin, erythromycin and gantrisin were used, either alone or in combination. These drugs did not appear to modify the course of the illness.

In nine instances salicylates alone were administered. In the earlier cases salicylates were not given until after a period of observation, whereas later the drug was instituted within twenty-four hours of onset of the illness. Prompt amelioration of pain and fever resulted and the duration of these episodes of the postcommissurotomy syndrome appeared to be distinctly abbreviated. Salicylates also seemed to accelerate the disappearance of C-reactive protein from the patient's blood. (Figs. 4 and 5.)

Six patients received a combination of antibiotics plus salicylates. In most of these cases the antibiotics were given early in the illness; and when these failed to modify the course, salicylates were administered, often with dra-

A.R. of 21 yrs. Mitral stenosis PCS Max. daily ******* Chest pain CRP Aspirin (qm./day) Antibiotics WBC 11 11.5 12 14 12 14 12.75 9.5 (thousands) ESR (mm/hr) Westergren A50 (units) 65 Days post-operative Fig. 4. E.C. of 39 yrs. Mitral stenosis PCS (°E)



matic improvement. No patient in this series received cortisone or adrenocortical hormone.

Laboratory Studies of the Immediate Postoperative Period. Study of the postoperative courses of eighteen patients* after mitral commissurotomy and of six patients* following a variety of procedures for correction of non-rheumatic vascular abnormalities failed to elucidate causes for the postcommissurotomy syndrome. The postoperative course of the rheumatic patients

TABLE XI
STUDY OF IMMEDIATE POSTOPERATIVE PERIOD IN EIGHTEEN
PATIENTS FOLLOWING MITRAL COMMISSUROTOMY AND SIX
PATIENTS FOLLOWING CORRECTION OF NON-RHEUMATIC
CARDIOVASCULAR DISORDERS

	Rheu- matic Heart Disease (Pa- tients)	Contro Group (Pa- tients)
Period of observation in hospital		
(days):		
1-14	0	4
15-28	10	2
29-56 Persistence of CRP postoperatively (days):	8	0
1-14	3	5
15-28	13	1
29–56	2	0
Maximum titer of CRP:		
low	3	1
moderate	10	0
high	5	5
Persistence of fever postoperatively		
(days):		
1–7	7	5
8-14	3	0
15-56	6	1
Postoperative white blood cell count:		
normal	1	2
elevated	12	1
Postoperative ESR:		
normal	0	2
elevated	8	1
Postoperative complications:		
Pericardial friction rub	9	0
Left hemothorax	4	0
Paroxysmal auricular fibrillation	3	0
Left pleural effusion	3 2 2	0
Embolism	2	0
Right subdeltoid bursitis	1	0
Left pleural empyema	0	1

was more protracted (Table XI); fever persisted for longer periods. Antibiotics were freely used in both groups. Where data were available the white blood count and erythrocyte sedimenta-

^{*} Two additional patients were included for study of the laboratory data in the immediate postoperative period.

^{*} Three cases of patent ductus arteriosus and one each of coarctation of the aorta, tetralogy of Fallot and abdominal aortic aneurysm.

tion rate were generally more elevated in the mitral commissurotomy group.

The C-reactive protein appeared within twenty-four hours following surgery in both groups. Although no differences in the level of C-reactive protein were evident, it persisted for longer periods in the rheumatic patients. The abnormalities of laboratory data in the rheumatic patients could be ascribed in large measure to more numerous postoperative complications.

CASE REPORTS

CASE I. A. R., a twenty-one year old Puerto Rican man, had acute rheumatic fever at the ages of seven and eight. At the age of twenty progressive congestive heart failure, manifested by dyspnea, orthopnea and ankle edema, appeared. He was admitted to The Mount Sinai Hospital where appropriate cardiac studies were performed. Mitral stenosis, with enlargement of the left auricle and right ventricle, was demonstrated and cardiac catheterization studies indicated pulmonary hypertension. Although digitalis, salt restriction and diuretics afforded some improvement, the patient was readmitted to the hospital and finger-fracture mitral commissurotomy was performed. The left auricular appendage contained multiple cellular infiltrates characteristic of Aschoff bodies. The postoperative course was uncomplicated, and at the time of discharge from the hospital on the thirty-third postoperative day the patient was afebrile and asymptomatic. Preoperative data concerning the antistreptolysin-O and C-reactive protein are lacking but it was determined on the day of discharge that C-reactive protein was absent from his blood.

The following day sharp, sticking, non-radiating left anterior chest pain suddenly appeared. Fever of 101°F. ensued; the patient complained of sweats, dizziness, nausea and some dyspnea. The symptoms persisted and he was readmitted to the hospital on the third day. The patient was in moderate respiratory distress. Dullness, diminished breath sounds and fine moist rales were present at the lung bases, more marked on the left. A left pleural friction rub was noted. The heart was enlarged; the rhythm was regular and the rate 120 per minute. The blood pressure measured 110/75 mm. mercury. The second pulmonic sound was accentuated, reduplicated and louder than the second aortic sound. The heart sounds were of good intensity. A mid- and late diastolic rumbling murmur was heard at the apex, with transmission to the axilla. A coarse, grating friction rub was heard throughout systole and diastole in the third and fourth intercostal spaces to the left of the sternum. There was no evidence of cardiac embarrassment or failure.

Laboratory tests disclosed normal urinary findings and a normal hemoglobin. The white blood count was 11,000 cells per cu. mm. and the erythrocyte sedimentation rate was 50 mm./hour (Westergren). Blood cultural studies were sterile. Roentgenographically, there was considerable increase in cardiac size as compared with previous postoperative films, and the amplitude of cardiac pulsations was diminished fluoroscopically. Except for the presence of a left pleural effusion there were no abnormalities in the lungs. The electrocardiogram showed sinus tachycardia, right axis deviation and wide notched P waves. As compared to previous findings, the S-T segments in the precordial leads were depressed and the T waves inverted.

Figure 4 illustrates the patient's course during his hospital stay. The temperature rose to levels of 103°F. Chest pain persisted, was aggravated by respiration, and shifted from the left to the right side with radiation to the shoulders. The pulmonary signs appeared in one lung and then in the other. The pericardial friction rub disappeared but leukocytosis persisted and electrocardiographic changes consistent with the diagnosis of acute pericarditis were noted. Penicillin and aureomycin were given and after twelve days the fever abated and the patient appeared well.

Despite continued administration of antibiotics, the postcommissurotomy syndrome recurred on the fifty-fifth postoperative day. This episode was similar to the preceding attack. Antibiotics were discontinued on the fiftyeighth postoperative day. The syndrome persisted and aspirin therapy was instituted five days later. Prompt relief of the fever and chest pain ensued; the heart size diminished, and the pulmonary signs and pleural effusions disappeared. The patient felt well and was allowed out of bed, without incident. On the eightyfirst postoperative day aspirin was discontinued. The patient has been afebrile and asymptomatic for the ensuing fifteen months.

Serial C-reactive protein determinations have been useful in the management of this patient. On the twenty-eighth postoperative day, prior to the onset of the postcommissurotomy syndrome, C-reactive protein was absent from the

patient's blood. Large amounts of it appeared during the first febrile episode, associated with slight increase of the antistreptolysin-O titer. The C-reactive protein did not disappear entirely from the patient's blood following temporary subsidence of the first episode of fever. Prompt increase of the level of C-reactive protein occurred with recrudescence of the postcommissurotomy syndrome. The high level persisted throughout the second episode; after aspirin treatment was instituted, despite persistent leukocytosis and elevated erythrocyte sedimentation rate, the C-reactive protein disappeared promptly from the patient's blood. While the patient received salicylates he felt well and no C-reactive protein was detected in his blood. When salicylates were discontinued, C-reactive protein reappeared in the blood for one week, despite the absence of symptoms, fever or other abnormal laboratory results. In the ensuing fifteen months the C-reactive protein has been consistently absent from blood samples taken at weekly or monthly intervals.

Comment. This typical example of the postcommissurotomy syndrome illustrates the apparent salutary effect of salicylates. The C-reactive protein was shown to be an index of activity of the postcommissurotomy syndrome; changes in the amount of this protein in the blood accurately reflected the changing clinical state. The prompt disappearance of C-reactive protein following salicylate therapy, in contrast to its persistence after treatment with antibiotics alone, suggests either that salicylates suppress the pathologic process responsible for the production of C-reactive protein or that they suppress the precipitation of C-reactive protein directly.

CASE II. E. C., a thirty-nine year old Negro male, had acute rheumatic fever in early childhood and had known of a heart murmur since that time. He had had increasing dyspnea for one and a half years. Physical examination revealed an enlarged heart with basilar pulmonary rales. Auricular fibrillation was present, the pulmonic second sound was accentuated and auscultatory indications of mitral stenosis were in evidence. In addition, there was an inconstant, blowing, high-pitched diastolic murmur located in the third intercostal space to the left of the sternum, radiating to the lower substernal area. The blood pressure was 100/70 mm. of mercury. The chest x-ray revealed enlargement of the left auricle and right ventricle and some question-

able enlargement of the left ventricle; these findings were confirmed by angiocardiography. The electrocardiogram revealed auricular fibrillation and right axis deviation. Cardiac catheterization indicated pulmonary hypertension. The hemoglobin was normal. Leukocytosis of 12,000 was present but the erythrocyte sedimentation rate was normal, the C-reactive protein was negative and the antistreptolysin-O titer was 317 units. Finger-fracture mitral commissurotomy was performed without complication. The left auricular biopsy contained several Aschoff bodies. The postoperative course was uncomplicated (Fig. 5) and fever disappeared after eleven days. The C-reactive protein became moderately elevated but disappeared from the patient's blood by the eighteenth postoperative

On the twenty-fifth postoperative day pressing right and left upper anterior chest pain suddenly appeared, associated with substernal and epigastric discomfort, nausea, vomiting and temperature of 104°F. Fine, moist, inspiratory rales appeared at both lung bases. Radiographically, no pulmonary infiltrations were demonstrated. The white blood count had fallen to 12,000 and the sedimentation rate to 58 mm./ hour. On the other hand, the C-reactive protein reappeared in the patient's blood within fortyeight hours. Aspirin was given in daily doses of 2.4 gm., with symptomatic improvement within a few days. The level of C-reactive protein diminished and finally the abnormal protein disappeared after ten days. Suppressive aspirin therapy was maintained.

On the fifty-third postoperative day the patient experienced recurrence of the postcommissurotomy syndrome unassociated with fever. The physical findings were similar to those of the preceding attack. Although the white blood count and antistreptolysin-O were unaltered and there was a mild rise of the erythrocyte sedimentation rate, the C-reactive protein appeared in moderate amount in a blood sample examined on the second day of the illness. The dose of salicylates was increased, the pain remitted and the patient improved. A sample of blood taken on the third day of illness contained no C-reactive protein. Subsequent blood samples also were free of this protein. The patient has continued on salicylate suppressive therapy since discharge from the hospital.

Comment. In this patient salicylates appeared favorably to modify the postcommissurotomy

syndrome. The second episode developed despite aspirin suppressive therapy but was mild and of short duration. In this case, too, the C-reactive protein was useful as a laboratory guide of activity of the postcommissurotomy syndrome.

DISCUSSION

The reported incidence of the postcommissurotomy syndrome varies from 10 to 38 per cent of operated cases. 3,9-12 Many episodes of this syndrome undoubtedly have not been recognized because of lack of awareness of patient or physician. On the other hand, variation in surgical technic may account for some differences of incidence in different centers.

The clinical findings of the postcommissurotomy syndrome in this group of cases correspond to those published elsewhere. The signs and symptoms can be ascribed to recurrent bouts of pericarditis and pleuritis. Associated arthritis occurred in three cases reported by Soloff et al. and in one case in the present series.

Information concerning the laboratory data in this illness has been sparse. Leukocytosis, rapid erythrocyte sedimentation rate and negative bacteriologic studies have been reported in five patients. 10 Radiographic studies demonstrated cardiac enlargement and electrocardiographic investigations revealed changes compatible with pericarditis. These findings have been confirmed in our patients. In addition, it has been demonstrated that the antistreptolysin-O titer did not change during the postcommissurotomy syndrome, indicating that beta-hemolytic streptococcal infection did not precede the illness. This is confirmed by the failure of chemoprophylaxis to prevent the occurrence of the postcommissurotomy syndrome. 9,12

Controversy has arisen in regard to treatment. There is general agreement that antibiotics do not modify the illness. Janton et al.⁷ and Wood¹¹ believe that salicylates exert no influence on the course of the illness whereas others^{3,9,10,12} have reported a favorable-action of this drug. Results obtained in the present series support the latter view. Moreover, salicylates appear to suppress postoperative morbidity due to the post-commissurotomy syndrome effectively. Adrenocortical hormones have been found efficacious by others in the treatment of the postcommissurotomy syndrome.¹⁰

Considerable speculation has arisen concerning the etiology and pathogenesis of the post-

commissurotomy syndrome. At one time pulmonary embolism was considered the responsible cause. The presence of pericarditis, the absence of prominent hemoptysis, the failure of radiographic confirmation of pulmonary emboli, the clinical course and the self-limited nature of the illness militate against this hypothesis. Bacterial infection was similarly suspected. However, bacteriologic studies have been negative and antibiotics have failed to modify the course of the disease.

Direct trauma to the pericardium appears not to be the sole cause since other surgical procedures involving the pericardium do not induce a similar reaction. Cardiopericardiopexy^{17,18} performed in patients with coronary artery disease affords an adequate control experience in this connection. During this operation the pericardium is opened, foreign material is inserted and the pericardium is then loosely closed. Postoperatively a foreign body reaction ensues with fever, pericarditis and pneumonitis, lasting approximately one week. Thompson¹⁹ has followed up 150 cases for several years postoperatively without observing any syndrome resembling that following mitral commissurotomy. Reports concerning surgical correction of congenital heart disease have consistently failed to mention the occurrence of a similar complication. Recently, however, Likoff²⁰ has observed somewhat similar febrile illnesses in six adult patients following surgical correction of congenital pulmonic stenosis and interatrial septal defect. This communication provides the only indication yet obtained that an illness similar to the postcommissurotomy syndrome may occur after cardiac surgery in non-rheumatic patients.

The occurrence of this illness almost exclusively in the rheumatic patient suggests that some fundamental feature of the rheumatic process may contribute to its pathogenesis. It has occurred in one of our patients with mitral stenosis (excluded from the present series) in whom only pericardiotomy was performed; because of technical considerations at operation the heart was not incised. A typical episode of the postcommissurotomy syndrome appeared three weeks later. In addition, the postcommissurotomy syndrome has been observed following surgical repair of rheumatic aortic stenosis, although with less frequency than following mitral commissurotomy.²⁰

Reactivation of acute rheumatic fever following mitral commissurotomy has occurred very infrequently, with a reported incidence varying from 0 to 7 per cent.^{2,3,10,12,21} In a measure, this can be ascribed to careful selection of patients. Many groups consider rheumatic activity an absolute contraindication to operative intervention^{1,4,22} whereas others^{5,6,23} have operated upon patients with unequivocal signs of rheumatic activity, without exacerbation of the rheumatic process.

Despite the lack of clinical or laboratory evidence to indicate the presence of rheumatic activity, 25 to 40 per cent of all auricular appendages amputated at operation contained Aschoff bodies. 16,24-28 Kuschner and Levieff29 have demonstrated by appropriate postmortem studies that the presence of Aschoff bodies in the left auricular appendage implies that lesions are very likely to be present elsewhere in the heart. On the other hand, the absence of Aschoff bodies in the appendage does not preclude the possibility of activity elsewhere in the heart.29 However, the clinical significance of these histologic findings has been questioned28 and present evidence30 is insufficient to prove or disprove a relationship between the finding of Aschoff bodies in the auricle and clinical rheumatic activity. It has been shown in the present study that the postoperative course and the incidence, manifestations and duration of the postcommissurotomy syndrome do not show any discernible correlation with the presence or absence of Aschoff bodies in the auricular specimens.

Accounts of the natural history of rheumatic fever and rheumatic heart disease have not heretofore alluded to any illness recognizable as identical with the postcommissurotomy syndrome. Chest pain occurs infrequently during acute rheumatic fever and rheumatic pleuritis was observed in only 2.5 to 14 per cent of cases studied by Wilson.31 Many similarities between rheumatic pericarditis and the postcommissurotomy syndrome are evident, however. Chest pain, evidence of fibrinous pericarditis without large effusions, left-sided pleuritis and pulmonary rales were noted by Thomas et al.32 in their detailed study of pericarditis occurring during the course of acute rheumatic fever. They stated that "dry pericarditis appeared to be relatively benign; it invariably occurred during the first month of rheumatic activity, caused no electrocardiographic changes, was of short duration, and had no effect on prognosis." The postcommissurotomy syndrome similarly appears to

be benign without adversely effecting prognosis. In cases of rheumatic pericarditis, however, both endocarditis and myocarditis are usually present at least in children; in the postcommissurotomy syndrome apparently isolated pericardial involvement is present. It is of interest that Soloff reported one patient who died during an episode of the postcommissurotomy syndrome and manifested active rheumatic carditis at necropsy.

The present view concerning the pathogenesis of the postcommissurotomy syndrome proposes that the syndrome may represent bouts of an exudative inflammatory process involving the pericardium and pleurae. This process is believed to develop in response to trauma sustained at the time of surgery and, in addition, as a reaction to foreign material introduced at that time. Since these reactions have been limited to date almost exclusively to patients with rheumatic heart disease, it is possible that the rheumatic process may be involved in some as yet undetermined way in the pathogenesis of this illness. The salutary effects of salicylates and adrenocortical hormones could be ascribed to their suppression of the inflammatory reaction.

In this investigation the test for C-reactive protein has proved useful as a laboratory index of activity of the postcommissurotomy syndrome. The C-reactive protein is an abnormal protein absent from the blood of normal people but appearing as an acute phase response in a variety of abnormal conditions such as trauma, infections, necrosis, neoplasia and granuloma formation.33 It has been characterized by free electrophoresis as a beta globulin and is apparently combined with lipid in vivo. 34 Its major application has been in acute rheumatic fever, 15,35 where it has been found to be an excellent indicator of the inflammatory reaction and hence a useful guide in management. Recently36 it has been found to appear in the blood following acute myocardial infarction and even with congestive heart failure.37 Despite its lack of specificity, however, the determination has often proved more useful than other non-specific indicators such as the erythrocyte sedimentation rate or white blood count.

SUMMARY

The postcommissurotomy syndrome developed in ten of sixteen patients ten days to seven months following mitral commissurotomy. Seven patients had multiple attacks.

The syndrome consisted of chest pain and fever together with less prominent and frequent cough, hemoptysis, dyspnea and arthralgias. Evidence of pericarditis and pleuritis was obtained, with leukocytosis and elevated erythrocyte sedimentation rate. Bacteriologic studies yielded negative results. Penicillin prophylaxis was ineffective and antibiotics failed to modify the course. Salicylates appeared to abbreviate the illness.

No significant change in the antistreptolysin-O titer occurred during this illness. The C-reactive protein was found to be the most sensitive laboratory test for the postcommissurotomy syndrome and the most useful in management.

The possible etiologic factors are reviewed. It is suggested that the postcommissurotomy syndrome represents a self-limited form of pericarditis and pleuritis induced by the trauma of surgery in patients with rheumatic heart disease.

Salicylate suppressive therapy is recommended for all postcommissurotomy patients. The C-reactive protein test is suggested as a useful and sensitive test for the activity of the postcommissurotomy syndrome.

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Seminars on Antihypertensive Drugs

Blood Pressure Reduction in Arterial Hypertension by Hexamethonium and Pentapyrrolidinium Salts*

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ANY distinct pathologic processes lead to hypertension but, irrespective of the primary cause, subjective and objective clinical manifestations arise which are due to the high blood pressure as such, or to the associated vasoconstriction.1 In nephritis, pyelonephritis, pheochromocytoma, Cushing's syndrome and aortic coarctation, the nature of the primary pathologic process associated with the hypertension is evident, even though the precise mechanism by which the blood pressure has become elevated remains obscure. In essential hypertension symptoms and signs appear to be restricted to those which can be attributed reasonably to the consequences of high blood pressure as such, or vasoconstriction. Except in so far as they induce clinical manifestations through blood pressure elevation, the basic pathologic processes responsible appear to be comparatively harmless. There is some evidence^{1,2} that essential hypertension is not due to any single or simple primary cause. Perhaps it may originate in some cases from the simple over-activity of physiologic processes, whereas in others pathologic changes such as renal arteriosclerosis may be primary. It has been suggested that blood pressure increases tend to be selfperpetuating.1,3 This may occur as the result of such changes as inelasticity of large arteries, exaggerated contraction of hypertrophied arterioles, secondary renal changes and from factors not yet known. Such an interpretation of the significance of high blood pressure offers a logical justification for treatment by strict control over blood pressure levels. Blood pressure elevation is thus regarded as an intermediate cause common to all types of hypertensive dis-

order; the cause of what are rightly called hypertensive signs and symptoms. Those who have regarded hypertension as being a compensatory process which serves to maintain a flow of blood through narrowed blood vessels have tended to regard blood pressure reduction as mere symptomatic treatment involving the potential danger of undue restriction of the blood supply to important organs such as brain, heart and kidney. There are individual patients in whom these objections are valid and in whom undue reduction of the blood pressure causes a temporary hemiplegia or aphasia, anginal pain or impaired renal excretion. Fortunately, treatment of high blood pressure of substantial degree need never be withheld for the fear of cerebral, renal or cardiac complications though, as will be seen later, it should be postponed for a time (arbitrarily six weeks) after cerebral thrombosis or coronary thrombosis.

REASONS FOR METICULOUS CONTROL OF BLOOD PRESSURE REDUCTION IN SEVERE HYPERTENSIVES

The paramount question is: Does blood pressure reduction relieve hypertensive manifestations? Consideration of what is or is not practicable in everyday medicine should not obscure this issue. Some evidence on this was obtained in severe hypertensive patients whose blood pressures were maintained at a normal level for periods up to ten days without intermission by subcutaneous hexamethonium bromide using a continuous injection machine. The patients were seated in cardiac beds so as to enhance blood pressure falls. Following the period of continuous control, frequently repeated subcutaneous injections were used to maintain the

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blood pressure near to normal for much longer periods. Trained technicians measured the blood pressures at fifteen-minute intervals throughout the day, and occasional readings were made at night. On regimens started by continuous injection and maintained by repeated subcutaneous injections, there was rapid improvement and ultimate disappearance of papilledema, retinal exudates and hemorrhages. In about threequarters of patients with such complaints, cardiac asthma and severe hypertensive heart failure cleared, without recourse to other measures such as digitalis, mersalyl and salt-free diet, to the extent that such patients could climb stairs without appreciable breathlessness. Patients who had gone into heart failure while still on digitalis were relieved of the heart failure by blood pressure reduction using methonium salts, but without otherwise altering the regimen. Such degrees of objective improvement were obtained by methods not readily maintained under everyday conditions but they show that dramatic improvements follow restoration of a normal blood pressure.

The writing of this review is influenced by the author's firm opinion that the aim of treatment in most severe hypertensive states should be the reduction of the blood pressure to as near 120/80 and for as much of the twenty-four-hour day as is practicable.

EFFECTS OF HEXAMETHONIUM AND PENTAPYRROLIDINIUM

The hypotensive actions of hexamethonium and pentapyrrolidinium, as far as they have been tested, appear to be similar except for differences in the size of doses required to produce equivalent blood pressure reduction and in the duration of the blood pressure reduction. Up to the present there is more detailed information about hexamethonium. Attention was first directed to the pharmacology of the methonium salts by Chou and de Elio, ⁵ Barlow and Ing, ^{6,7} Paton and Zaimis ^{8–10} and Paton. ¹¹

Hexamethonium

Circulatory Effects of Hexamethonium Salts. It was soon evident that penta- and hexamethonium salts induced blood pressure falls in animals and in man. After penta- or hexamethonium salts, although the blood pressure falls, there is an increase in the blood flow through the feet¹²⁻¹⁴ and arms, 15 but to a lesser degree in the latter. 16 The difference in degree of vasodilatation is not

solely due to posture and may be because the legs have a greater sympathetic vasoconstrictor tone than the arms.¹⁷ With subjects in the sitting posture hexamethonium leads to an increase in leg volume but arm volume may increase or diminish.¹⁸ X-ray pictures show that sometimes, in the erect posture, lung congestion is diminished during blood pressure reduction from an injection of hexamethonium bromide.¹⁸

The pulmonary artery pressure is usually reduced following injections of hexamethonium bromide in the course of catheter studies. 19-21 Injections of hexamethonium salts reduce the venous pressure, measured in the arms or by observation of the neck veins. 18,22,23 The fall may be 1 to 6 cm., and the venous pressure fall may precede blood pressure reduction. 18,22 Substantial falls of venous pressure may be noted in congestive heart failure.

The blood pressure fall is much influenced by posture, being greatest when the patient is standing, intermediate when sitting and least in the lying posture. 16,18,22,24-26 Doses safe for routine clinical purposes may not reduce the blood pressure much with the patient lying flat, but when the patient stands or even sits, the blood pressure may fall from a hypertensive level to 85/55. Even in the lying posture if much larger doses are given, the blood pressure may be reduced in most patients to well below the basal pressure. The falls of blood pressure are also greater after methonium than after amytal, 28 and greater after methonium than after a seconal sedation test. 29

Ordinarily, blood pressure falls are greater in hypertensives than in normotensives and are usually large in patients after sympathectomy²⁷ and after a salt-free diet. 18.30-32

Some changes in blood pressure level appear to depend on interference with the capacity of the sympathetic nervous system to perform its normal circulatory reflex functions. Thus in the erect posture the blood pressure falls because of the absence of sympathetic vasoconstriction. In patients under the action of methonium salts an additional fall of blood pressure usually follows meals, presumably due to uncompensated splanchnic dilatation.27 Small blood losses of 250 cc. may cause substantial blood pressure falls when patients are under the action of methonium salts, presumably due to absence of compensatory vasoconstriction.33 The occurrence of collapse with congestion of both lower limbs33 is apparently an analogous

phenomenon. The overshoot of the blood pressure which normally follows a drop in pressure during the Valsalva experiment is abolished, ²⁶ and so also is the overshoot of the blood pressure when a patient is tilted back quickly from the vertical to the horizontal position. ²⁶ The response to the cold pressor test is usually diminished. ²⁴

If a patient whose blood pressure has been greatly reduced by hexamethonium stands in a warm swimming bath with water up to the chin, the blood pressure rises at once almost to the level prior to the dose of hexamethonium. The counter-pressure of the water on the external body surface neutralizes the effect of gravity. A hypertensive patient's blood pressure can be regulated to almost any desired level by increasing or decreasing the depth of immersion in the swimming bath.22 Application of positive pressures in other ways has a similar effect. A degree of gravitational hypotension from the drug is present in the horizontal posture since, even in this posture, neutralization of gravity by immersion in warm water causes a slight rise of blood pressure.22 The effect of negative pressures applied to the external body surface (below nipple level) was studied using a pressure chamber. After hexamethonium bromide negative pressures applied to the external body surface (below nipple level) by a pump-operated pressure-suction device cause great falls of blood pressure—in hypertensives as much as 100/40. The fall is smaller in the absence of hexamethonium, as sympathetic vasoconstrictor impulses can then neutralize the expanding force of the negative pressure upon blood vessels.

Pulse rates may increase or decrease after hexamethonium, 18,24,27 depending presumably on whether reflex acceleration from the fall of blood pressure or blockading of sympathetic acceleration predominates.

Other Effects of Hexamethonium Salts. Hexamethonium decreases the secretion of hydrochloric acid in the stomach. 34 Gastric motility is reduced, and with large initial doses there is radiologic evidence of decreased peristalsis and delayed emptying. 35 Severe constipation may follow both parenteral and oral administration 36-38 and may be interrupted by bouts of diarrhea. 39

The absorption of hexamethonium salts given orally is incomplete.⁴⁰ Hexamethonium is excreted by the kidneys, the clearance ratios of hexamethonium and inulin being very similar (1.1–1.2) indicating that excretion of hexa-

methonium is mainly by the glomeruli.⁴¹ The estimated renal plasma flow and the glomerular filtration rate are sometimes temporarily diminished in man during methonium hypotension.⁴²⁻⁴⁵ Miles et al.⁴⁶ found the renal plasma flow undiminished in acute studies. Ordinarily with continued administration there is no significant delay in renal elimination,^{45,47} but cases are on record in which nitrogen retention has increased during methonium hypotension.^{48,49}

Pentapyrrolidinium

The substance pentapyrrolidinium was synthesized by Libman, Pain and Slack.⁵⁰ Its pharmacology was studied by Wien and Mason.^{51,52} Studies in man of hexamethonium homologues led to recognition of the clinical potentialities of pentapyrrolidinium (Smirk^{53–55}). A comparison of the effects of pentapyrrolidinium and other homologues of hexamethonium was reported by Maxwell and Campbell.⁵⁶

In so far as they have been examined, the effects of pentapyrrolidinium on the circulation appear to be identical with those of hexamethonium but the dose is smaller and the duration of action longer with pentapyrrolidinium.

Postural hypotension occurs 53-57 and is of the same order as that encountered with other methonium compounds: pentamethonium, hexamethonium, M. & B. 1863 and pendiomide. A salt-poor diet exaggerates the postural hypotension.⁵⁷ In patients under the action of pentapyrrolidinium, meals produce additional falls of blood pressure. 54.57 The pulse rate may be increased or decreased. 53-56 Aqueous pentapyrrolidinium given in doses which reduce the blood pressure in the standing posture to approximately 120/80 cause falls of blood pressure ordinarily lasting four to six hours. The duration of the blood pressure fall is much extended when pentapyrrolidinium is dissolved in polyvinyl pyrrolidone 20 per cent, to which 0.5 per cent of ephedrine hydrochloride has been added in order to prolong absorption further by local vasoconstriction. 54,55 A full hypotensive dose of the retard preparation, which reduces the blood pressure in the standing posture to approximately 120/80, may exhibit some hypotensive activity for twelve hours or more. The duration of action of equally hypotensive oral doses is about the same. The trough of the blood pressure fall after an oral dose often occurs about two or three hours after administration on an empty stomach. As with hexamethonium, oral

doses are incompletely absorbed so that ten or twenty times the subcutaneous dose may be required to produce a corresponding effect by mouth.^{53–57} Pentapyrrolidinium is excreted in part by the kidneys and may be detected in the urine.⁵⁸

TOLERATION AND CROSS-TOLERATION

Drug toleration is an important feature of the action of hexamethonium salts. 27,59-64 If, in one day, two or three effective doses of hexamethonium are administered, a degree of toleration will already be apparent next day. With continued daily administration of oral or parenteral doses, sufficient to produce substantial blood pressure falls, drug toleration develops; and to maintain blood pressure falls doses must be raised daily or every few days for several weeks and thereafter less frequently. Ordinarily after two or three months the dose is comparatively stable or may even fall a little. If the administration of hexamethonium is discontinued, toleration is lost to an important extent in ten days. If administration is resumed, it should be at a lower dosage level.

Following the repeated administration of pentapyrrolidinium, either orally or parenterally, drug toleration also develops. Maxwell and Campbell⁵⁶ thought toleration developed at least as rapidly as with hexamethonium. Others have reported that drug toleration is much less than with hexamethonium or pentamethonium salts. ^{53-55,57} The hypotensive dose may be comparatively stable after six to eight weeks' treatment.

Following the repeated administration of hexamethonium, a cross-toleration is established to the subsequent administration of pentapyrrolidinium. Likewise, when pentapyrrolidinium is administered repeatedly, a measure of toleration develops to hexamethonium. 53,55 It is of interest that cross-toleration between M. & B. 1863, hexamethonium bromide and pentamethonium bromide is practically complete in that the ratio of activities before drug toleration is 2:1:1 and at all stages during the development of drug toleration, whichever drug is first administered, the relationship of the effective doses remains the same, viz., 2:1:1. Thus at any stage in the development of drug toleration with these three substances, it is possible to change from one substance to another and, provided the original ratio of the doses is preserved, the same hypotensive action results. 65 In contrast, the

degree of cross-toleration between hexamethonium bromide and pentapyrrolidinium is incomplete. 53,57 The initial effective dose of pentapyrrolidinium is usually one-fifth of the initial effective dose of hexamethonium bromide; but when toleration has been established, the effective dose of the pentapyrrolidinium is likely to be less than one-tenth of the equally hypotensive dose of hexamethonium bromide. When full toleration has been developed to either of these substances, it will be found on changing to the other substance that full toleration has not developed and further increase of dose will be required in order to preserve the full hypotensive effect.

PRELIMINARY INVESTIGATIONS

In addition to the clinical study of symptoms and physical examination, the following investigations are undertaken in almost all hypertensive patients: basal blood pressure using sedation, ^{66–68} 12-lead electrocardiogram, chest x-ray for cardiac silhouette, urea concentration, total non-protein nitrogen and retinal examination. The importance of the retinal grading ⁶⁹ requires no comment. In some instances pyelograms or tests for pheochromocytoma are required.

The basal blood pressure is of prognostic importance. It is reasonable to expect that those whose blood pressure does not fall at rest or in sleep are more prone to severe consequences than are those whose blood pressure level falls in an unstimulating environment. In patients with high basal blood pressures it is found that grade IV or grade III retinal changes, cerebral vascular accidents, cardiac enlargements, electrocardiographic signs and other adverse clinical manifestations occur more frequently than in those with equal casual blood pressures but lower basal pressures.⁷⁰

The basal blood pressure taken by the technic referred to aids the distinction between drug and placebo effects. Placebo administration, rest in hospital and diurnal sedation seldom decrease the blood pressure below the basal level, whereas effective hypotensive drugs do this.

CHOICE OF PATIENTS FOR TREATMENT

It is generally agreed that methonium salts are more suitable for severe than for mild hypertensive patients^{27,32,47,54,55,61,64,71-73} and that reduction of the blood pressure may be achieved in substantially all forms of hypertension. The first

choice for treatment are patients with hypertensive heart failure, cardiac asthma, breathlessness, severe headache, giddiness, repeated minor cerebral episodes and important degrees of hypertensive tenseness of temperament; nearly all such patients are glad to persist, even with a

better methods of blood pressure control becomes generally available, it may be reasonable to reduce the blood pressure levels in mild cases in the hope of preventing deterioration. Such a policy is at present based on conjecture but improvement with treatment in the clinical man-

TABLE I
INITIAL DOSES AND DOSAGE INCREMENTS OF METHONIUM COMPOUNDS

	In	nitial Dose (mg.)	by Inc	y Be Raised rements of mg.)	0	st Final Daily ose Used (mg.)	Average Duration	
	As Salt	As Methonium Ion	As Salt	As Methonium Ion	As Salt	As Methonium Ion	Significant Action (hr.)	
Pentapyrrolidinium bitartrate, oral Pentapyrrolidinium bitartrate "retard,"	20	8.9	20	8.9	1400	623	8-12+	
subcutaneous	3	1.34	0.5-1.5	0.22-0.67	140	62.3	8-12+	
Hexamethonium bromide "retard," subcutaneous	20	11.2	5-10	2.8-5.6	1200	672	3-5	
Hexamethonium bromide simple aqueous, subcutaneous	15	8.4	5	2.8	1200	672	2-3	
Hexamethonium chloride simple aqueous, subcutaneous.	12	8.8	4	2.9			2-3	
Hexamethonium bitartrate, oral	187	76.1	187	76.1	9000	3663	2-4	
Hexamethonium chloride, oral	125	92.5	125	92.5			2-4	

complicated regimen, and to tolerate side effects because of the relief from hypertensive symptoms. Patients with grade IV or grade III retinae should be accepted for treatment. 27.64.71.72 There is evidence that hypertensive patients with angina may obtain important decreases of pain 27.49.74.75 but in anginal patients blood pressures should not, at least initially, be reduced below 140/90 as excessive falls of blood pressure induce precordial pain. 26.27.75 In hypertensive patients with recent cerebral thrombosis it is probably wise to wait six weeks before starting treatment and then to avoid hypotension.

Renal disease does not contraindicate treatment. 27.32.47.49.55.63.64.71.76 If, however, it is thought desirable to lower the blood pressure in a patient with impaired renal function then the non-protein nitrogen should be determined on a number of occasions until it is evident that the nitrogen elimination remains satisfactory. 27.32.45.64 Improvements in renal function have been reported and also deteriorations. 48.49

The treatment of the milder hypertensives before hypertensive symptoms are present to a significant degree is a matter of policy. As the ifestations of severe hypertension offers hope that some sequelae of high blood pressure could be postponed, even prevented.

PRACTICAL DETAIL OF CONTROL OVER BLOOD PRESSURE LEVELS

There is no useful place in methonium treatment for a simple routine which ignores the individual response of the patient. 27,49,64 If a fixed dose of a methonium salt is given without regard to the development of drug toleration and without taking advantage of the postural hypotension induced by the drug, early doses are likely to be dangerous or disturbing and later ones ineffective; side effects will be more and relief of symptoms less.

Patients vary by 200 or 300 per cent in their sensitivities to methonium salts²⁷ but in one and the same individual changes of dose of as little as 10 per cent may make an important difference in the extent of the blood pressure fall. Hence great accuracy is needed in adjusting the magnitude of the dose to the individual requirement.³⁹ Table 1 sets out the initial doses of some methonium preparations for oral and subcuta-

neous use in ambulant patients. In patients over the age of seventy the initial doses should be divided by three. If a salt-poor diet has been given or the patient has previously had a sympathectomy, the dose should be halved.

The effectiveness of the doses given should be

devised which is applicable to all of them. The basic principle is that doses of the various preparations are adjusted with the object of inducing falls of blood pressure of the magnitude indicated in Figure 1. It will be seen that lines A, B and C in Figure 1 have in common that, at

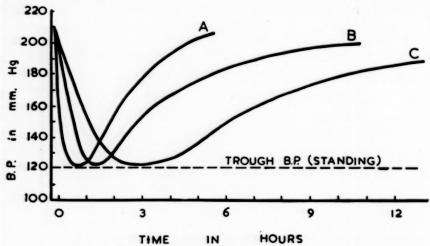


Fig. 1. Lines A, B and C indicate approximately the effects on the blood pressure taken in the standing posture of various methonium preparations referred to in the text. The figure is intended to show that, with all preparations used, the aim is to discover the dose which brings the blood pressure (standing) in the trough of the blood pressure fall down to 120 systolic. The diastolic pressure will then be satisfactory also.

judged by blood pressures measured in the erect posture. Initial doses will not always drop the blood pressure sufficiently. The dose should be raised by the increments indicated in the table until an effective dose is reached. To keep pace with the development of tolerance the dose must be raised at first daily, later less frequently, to maintain effective control. The development of full tolerance may take several months.

With subcutaneous injections accurate dosage requires the use of a tuberculin syringe graduated in 0.01 ml.; ^{49,55} by mouth small-dose tablets are used which may be divided accurately or, better, dissolved in water and a proportion measured. ⁵⁵ The gap between the dose which induces a sufficient fall in blood pressure and that which leads to uncomfortable side effects is a small one. Meticulous accuracy in dosage can be achieved by patients who are adequately instructed and such accuracy makes an important difference to their comfort.

The various methonium preparations used clinically differ in the magnitude of the effective hypotensive dose, in the duration of action of a single dose and in the method of administration, but their pharmacologic effects are sufficiently similar for a scheme of treatment to be

the trough of the blood pressure fall, the blood pressure is in the region of 120/85. Were the trough blood pressure (standing) to fall much below this level, the patient would feel faint and would have to sit down and rest at this time. The aim of treatment, therefore, is so to regulate the dosage that the blood pressure at the trough of the blood pressure fall is in the region of 120/85.

Line A indicates the approximate course of the blood pressure fall after subcutaneous injections of aqueous solutions of pentamethonium, hexamethonium or of M. & B. 1863, and of oral doses of these given on an empty stomach. With oral doses the trough of the blood pressure fall occurs a little later in time than is shown in the line A. Line B represents the action of injected hexamethonium or M. & B. 1863 dissolved in 20 per cent polyvinyl pyrrolidone with the addition of 0.5 per cent ephedrine hydrochloride, or of a simple aqueous solution of pentapyrrolidinium. Line C represents approximately the effect of a subcutaneous injection of pentapyrrolidinium dissolved in 20 per cent polyvinyl pyrrolidone with the addition of 0.5 per cent ephedrine hydrochloride, or of oral doses of pentapyrrolidinium.

Ideally the adjustment of doses should be in terms of tests lasting several hours or all day^{27,49,55,61} in which the blood pressure is measured at, say, half-hour intervals. The blood pressure should be measured in the standing posture. ^{18,38,48,61} The tests may be made in the hospital^{32,38,61,72} or in a special outpatient clinic. ^{49,55} The object is to determine the lowest level to which the blood pressure falls with the patient in the standing posture. This is the trough blood pressure (standing). If hypotensive symptoms occur, they will be maximal at this time.

When repeated tests are impracticable it is found that an approximation to the ideal trough blood pressure (standing) can be obtained, without the use of a sphygmomanometer, by increasing the dose one increment at a time until the patient feels slightly faint in the erect posture. ^{49,54,55} The correct dose is, in practice, one or at the most two increments (Table 1) less than the dose which induces a feeling of faintness when the patient is standing quietly at the time of maximum drug action. Such doses are entirely safe; for if the patient adopts the sitting or lying posture, the blood pressure rises at once.

It should be emphasized that the degree of control over blood pressure levels is far more satisfactory when it has been adjusted in terms of hypotensive symptoms occurring in the erect posture than when attempts are made to regulate the dose in terms of casual blood pressure measurements. Routine casual blood pressures, even when taken at a fixed time after a dose, are confusing as a basis for dose adjustment except when the blood pressure is found to be low. 59,61,77

The main difficulty with control by symptoms is that a few patients have no warning symptoms of hypotension and blackout suddenly. Fortunately, this is an unusual reaction and easily recognized when it occurs.

Attempts to avoid all risks of inconvenient hypotension by reducing the dose not only decrease the extent of the blood pressure fall but shorten its duration. It is fundamental to realize that, with methonium salts, it is necessary to produce a fall of sufficient degree in order to produce a fall of sufficient duration.

EFFECT OF BLOOD PRESSURE REDUCTION ON THE CLINICAL MANIFESTATIONS OF HYPERTENSION

For many years it has been the custom to relate triumphantly the improvements in symptomatology which follow the administration of placebos in a hospital environment. If, however,

blood pressure reduction leads directly to improvement in hypertensive manifestations, the effect of reassurance, placebos and other simple means of reducing nervous tension may act to some extent through the intermediation of blood pressure decrease.

Unfortunately such improvements are seldom sufficient in degree in moderate cases, or helpful with the more severe manifestations. That mental processes increase or decrease symptoms in hypertension need not be doubted. Some of our patients, however, who anticipated methonium treatment but received initially a placebo, exhibited dry mouth and complained that vision was blurred so they could not read a newspaper. It would be unwise to conclude therefrom that the blurring of vision and dryness of the mouth which follow the administration of active methonium compounds are representative of the action of an inactive substance upon the imagination.

The relief of severe hypertensive symptoms by effective methonium treatment is of an entirely different and higher order than the relief which is ordinarily obtained from placebos or substances such as potassium thiocyanate. Objective manifestations are more readily assessed.

Retinal Changes. Improvements in the retinal picture have been recorded by many observers. Decrease or disappearance of papilledema during blood pressure reduction by methonium compounds has been noted. 18.27.28.32.37.61.64.78.79 In our experience the proportion of patients with papilledema who have lost this clinical manifestation has increased with improvement in the degree of control over the blood pressure, recent figures being twenty-one of twenty-three patients who were on effective treatment for five months or more. 79

With good control over the blood pressure level soft exudates ordinarily clear rapidly. 27,32,37,61,78 Hemorrhages disappear 27,37,61,78 but hard exudates with star-shaped macular figures seldom disappear with less than six months' effective treatment and may take twelve months. 79 Disappearance of excessive vasoconstriction in retinal arteries is usual. We have not been able to report disappearance of such arterial changes as arteriovenous nipping and waist-like constriction of retinal arteries.

Hypertensive Heart Failure, Cardiac Asthma and Breathlessness. Several observers comment on the relief of congestive heart failure, cardiac

asthma and breathlessness. ^{27,32,36,48,64,72,80,81} Increase in vital capacity and decreases in circulation time have been noted by Kelley, Freis and Higgins. ²³ It has been our experience that three of four patients with blood pressures over 200/120 may be relieved of hypertensive heart

sels. 82.83 A non-committal report by Smirk and Alstad²⁷ of improvement in anginal pain was followed by a more detailed study by Doyle and Kilpatrick⁷⁵ which makes it evident that important relief of anginal pain occurs in many patients with adequate control over the blood

TABLE II
OCCUPATIONAL STATE OF MALIGNANT HYPERTENSION PATIENTS UNDER TREATMENT

Case No.	Sex	Additional Clinical Features before Treatment	Age Starting Treatment	Occupation during Treatment	Months Survived or Treatment	
	1	Leading a Pr	oductive Life			
41	М		48	Accountant	48	
53	M		46	In general medical practice	54	
204	M	Left ventricular failure	45 57	Railway employee	35 34	
207	M	Left ventricular failure		Engineer; active		
306	M	Left ventricular failure; one leg amputated	55	Wire-mattress maker	25	
336	M	Minor cerebral accident	47	Farmer	25	
361	M	Cerebral accident; recovering from aphasia	47	Coppersmith	22	
382	M	Encephalopathic attacks	43	Garage work	19	
400	M	Left ventricular failure	41	Priest; educational work	16	
E7	M	Left ventricular failure	45	Farmer	32	
124	F	Subarachnoid hemorrhage	46	Housewife	43	
220	F	Encephalopathic attacks	63	Housewife		
357	F	Left ventricular failure	52	Housewife	20	
734	F	Aortic incompetence	36	Housewife	14	
	1	Incapacitated by Conditions Ar	ising before Tree	atment Started		
364	М	Cerebral vascular accident	44	Not working; stroke	20	

failure, cardiac asthma and breathlessness by blood pressure reduction using methonium compounds without recourse to digitalis, mersalyl or salt-free diet. In addition, patients who had gone into heart failure while still on digitalis have recovered on effective methonium treatment and without alteration in digitalis dosage or other medication. We regard this as objective evidence that the blood pressure falls have been responsible for the clinical improvements. Failure to obtain improvements of this order have been, in our experience, the result in almost all cases of inadequate control over the blood pressure level, being the result of such divergence from the regimen as inability to maintain the sitting posture during the night and inadequate dosage.

Decrease in Anginal Pain. It has been stated that at least some patients who develop pain on effort in the course of hypertensive disease have no actual narrowing of the coronary blood vespressure level. Others have also noted improvement in angina. 48.74

Changes in Heart Size and Electrocardiogram. Decreases in heart size may be of a striking character when patients with hypertensive heart failure are relieved of their symptoms by blood pressure reduction. Decrease in heart size in the absence of congestive heart failure is much less striking. In general, however, severe hypertensives whose x-ray pictures are repeated following methonium administration are more likely to show decrease than increase in heart size.⁷⁹

Electrocardiographic improvements were reported by Smirk and Alstad²⁷ and have been referred to by others. ^{32,48,71,72,74} Doyle⁸⁴ analyzed seventy-five patients who had been treated by hexamethonium for periods up to three years. He noted decreases in the voltage of the R and S waves, inverted T waves in left ventricular leads became less inverted or positive, and

elevated S-T segments became isoelectric. Electrocardiographic improvements were usual and deterioration unusual.

Life Expectancy. The clinical improvement in patients with advanced congestive hypertensive

be significant in our series, as is shown in Tables II and III. The survival periods are well beyond those expected for malignant hypertensive patients, and in both men and women most of these who were not disabled before treatment

TABLE III
OCCUPATIONAL STATE OF MALIGNANT HYPERTENSION PATIENTS TREATED UNTIL DEATH

Case No.	Sex	Additional Clinical Features before Treatment	Age Starting Treatment	Occupation during Treatment	Months Survived on Treatment	Cause of Death
	1	L	ading a Prod	uctive Life up to Time of Dec	ath	
123	М		56	Business executive	33	Obstructive jaundice; ?cerebral hemorrhage
371	M	Encephalopathic attacks	46	Furnace stoker	13	Cerebral hemorrhage
52	F	Severe heart failure	47	Housewife	14	Stroke
76	F	Severe heart failure	43	Housewife	10	Stroke
161	F	Two minor cerebral accidents	32	Housewife	28	Cerebral hemorrhage
716	F		36	Housewife	10	Uremia
		Leading	g a Partially	Productive Life up to Time of	Death	
51	М	Congestive failure; low I.Q.; osteoarthritis	59	Worked 2 years on farm; then old men's home, sweeping and cleaning	48	Coronary occlusion
			Incapacita	ated Until Time of Death		
49	F	Severe heart failure and renal insufficiency	52	Not working; lassitude	31	Bilateral pneumonia
		Died in	Hospital wi	thout Making Substantial P	Progress	
206	м		48	In hospital	6	Congestive heart failure suburemic state
227	M	Uremia	44	In hospital	2	Uremia
337	F	Diabetes; Kimmelstiel- Wilson disease	41	In hospital	4	Infection and uremia
			Died from A	Apparently Unrelated Causes		
40	М	Heart failure	52	Not working; mental confusion	48	Senile deterioration and dementia (cerebral arteriosclerosis)

heart failure in the absence of digitalis, mersalyl, salt-free diet or other measures provides a strong suggestion that life has been extended in these patients. In malignant hypertension prolongation of life and improved activity would seem to started are leading productive lives. Dr. John McMichael⁸⁵ informs us that his series of cases also indicates a statistically significant extension of life in malignant hypertension. The survival times of patients with grades III, II and I retinal

changes show improvement as regards life duration in the crude figures which we do not regard as statistically significant.

EFFECTS OF RESERPINE COMBINED WITH PENTAPYRROLIDINIUM

When given alone in conventional doses (up to 1 mg. daily) reserpine (an active principle of Rauwolfia serpentina) is usually a mild hypotensive agent probably unsuitable for the effective treatment of severe hypertensive patients. 86,87 In large doses, up to 9 mg. in a day, blood pressure falls exceeding 60/30 occurred in twelve of twenty patients but with prohibitive side effects.88 It is found, however, that a small set dose of reserpine, 0.5 mg. twice or thrice daily, enhances the response to pentapyrrolidinium so that smaller doses are effective. 73. 89,90 Side effects are consequently diminished. Experience with this combination in eighty patients who had been treated previously by oral pentapyrrolidinium alone indicates that in about sixty of these the combination was better either in respect of control over the blood pressure level or in freedom from side effects. The combination seems to us to be a better means of controlling the blood pressure level in severe hypertension than any other with which we have had experience.

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Needle Biopsy of the Kidney in the Diagnosis of Disseminated Lupus Erythematosus*

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THE clinical suspicion of disseminated lupus erythematosus is usually confirmed by finding the L.E. cell and by the diminished reduction of neotetrazolium by the patient's leukocytes.1 When such tests are negative the diagnosis is frequently not established until a postmortem examination is performed. It should be emphasized that a skin biopsy of a chronic lupus lesion does not in itself confirm or deny the existence of dissemination. The laboratory tests mentioned were negative in the case to be presented and therefore the initial impression of disseminated lupus erythematosus was less seriously considered. However, a renal needle biopsy established the diagnosis prior to the patient's death and this procedure may therefore be added to the more specific laboratory aids useful in establishing the diagnosis of lupus erythematosus disseminatus.

CASE REPORT

This was the first Duke Hospital admission of this forty-six year old Negro female, whose past health record was negative. Approximately four years before, when a mobile x-ray unit revealed the presence of an enlarged heart, she was told that she had high blood pressure. One year later she saw her physician because of fronto-occipital headaches and decreasing visual acuity, both of which persisted. She was told again of her high blood pressure. Approximately two years prior to this admission a pruritic, hyperpigmented rash developed over both malar eminences and spread to involve her forehead, ears and forearms. This rash was noted to be aggravated by sunlight which she was advised to avoid. Thinning of the scalp hair also developed. The skin changes fluctuated for a short time without

associated constitutional symptoms and later became quiescent. Six months to one year later she was told that she had kidney trouble and was advised to decrease her activities. Hematuria was apparently noted at this time. Six months prior to admission she first noted ankle edema which slowly progressed. During the early course of this development there was some history of dyspnea and non-radiating precordial discomfort. She was admitted to her local hospital for eleven days approximately four months later (October, 1953) with edema and hypertension. She was then treated with sodium restriction, bedrest and sedation which she continued. During the month prior to her hospitalization at Duke Hospital (December, 1953) she began to experience intermittent hematuria, anorexia, vague gastrointestinal discomfort and weight loss in spite of persistent anasarca. The patient denied any history of venereal disease, loss of blood from any orifice (except the urinary tract), fever or pleuritic pain.

The vital signs on admission were: a supine blood pressure of 210/124 in the arms and 230/ 140 in the legs, pulse 88, respirations 16, temperature 36.6°c., weight 69 kg. At this time the patient appeared to be chronically ill but in no acute distress. There was severe, generalized, pitting subcutaneous edema. Hyperpigmented confluent macular atrophic areas were noted on the skin mostly over the face (Fig. 1) but also on the arms and legs. Ophthalmoscopic examination revealed the presence of moderate arterial attenuation, A-V nicking and several exudates bilaterally. There was no significant adenopathy or venous distention. Lung fields revealed an elevated diaphragm and some medium moist basilar rales bilaterally. The heart was enlarged

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Fig. 1. Skin lesions of face.

to the anterior axillary line. There was a normal sinus rhythm. A₂ was louder than P₂. No significant murmurs were heard. The abdomen was protuberant and distended with fluid. No tenderness, organs or masses were noted. The remainder of the physical examination was within normal limits.

Upon admission to the hospital the patient's hemoglobin was found to be 8.3 gm. per cent. The white blood count was 6,500 and the differential count was essentially normal. The red cells were slightly hypochromic and platelets were adequate as seen in the peripheral blood smear. A sedimentation rate of 65 mm./hr. was recorded. The routine urinalysis revealed a specific gravity of 1.017, 4+ protein and a sediment with numerous red cells, 5 to 10 white cells and a moderate number of granular casts per high power field. A Gram stain of this sediment was negative but the initial urine culture showed the presence of Escherichia coli. Phenolsulfonphthalein excretion showed no dye during the first 15 minutes and a total of 22 per cent in two hours. The serologic test for syphilis was positive by complement fixation. The cardiolipin and Mazzini titers were 1. Blood chemistry determinations revealed the following: non-protein nitrogen, 72 mg. per cent; total protein, 5.3 gm. per cent (1.3 albumin and 4.0 globulin); cholesterol, 330 mg. per cent; P, 3.5 mg. per cent Ca, 6.5 mg. per cent; Na, 141.3 mEq./L.; K, 5.1 mEq./L.; Cl, 113.4 mEq./L.; and CO₂,

17.55 mEq./L. The electrocardiogram revealed a normal sinus rhythm with changes suggestive of left ventricular strain and/or ischemia. Roentgen studies of the skull were normal whereas those of the chest were interpreted as showing a moderately enlarged heart with a small amount of fluid at the right costophrenic angle and congestion of the lung fields. Numerous L.E. cell preparations were negative as was a leukocyte redox dye curve.

The patient was given the basic rice diet as treatment for both the manifest hypertension and the nephrotic syndrome. A skin biopsy was obtained which revealed changes compatible with but not diagnostic of lupus erythematosus. She was digitalized. Because of the urinary tract infection she was given gantrisin, and in treatment of the possible luetic infection she was given a course of penicillin. Later the negative result of a Neurath test was received. Therefore the routine S. T. S. was indicative of a biologic false-positive reaction. 2-4

In preparation for a renal needle biopsy a repeat blood non-protein nitrogen was found to be 48 mg. per cent. Intravenous pyelography revealed no evidence of excretion until 20 minutes, after which excretion was bilateral. The right kidney was then localized by x-ray and found to be of normal size. Bleeding, clotting and prothrombin times were within normal limits. A repeat urine culture revealed no growth. Electrolytes were in normal concentration. The hemoglobin was found to be 6 gm. The kidney biopsy was performed uneventfully approximately three weeks after admission. No referable complaints or significant increase in hematuria developed.

The biopsy (Fig. 2) revealed twenty-one glomeruli. Half of them were free from the capsule and half were attached to the capsule; of the latter, some were completely fibrotic. Rare genuine "adhesions" were present. The thickening and sclerosis of the basement membrane, both in the hematoxylin and eosin stain and in the periodic acid-Schiff stains, gave the "wire-loop" appearance. (Fig. 3.) The tubules showed low epithelium with dilatation. Hyaline droplets were present in occasional epithelial cells. Rare fine vacuoles were present but there was no large amount of fat as judged by the number of vacuoles. The larger vessels had thick walls. Hyaline arterioles were observed. Occasional lymphocytes and mild fibrosis occurred in interstitial tissue. The tubules of the



Fig. 2. Needle biopsy of the kidney in disseminated lupus erythematosus. Wire-loop appearance of glomerulus and glomerular adhesions can be seen.

Fig. 3. Glomerulus in the needle biopsy of the kidney showing the wire-loop change of disseminated lupus erythematosus.

medulla were not dilated. Occasional clear eosin-staining casts were noted. A stain for amyloid was negative. The diagnosis of lupus erythematosus was made chiefly on the basis of the wire-loop change. ^{5,6} Mention was also made of a mild degree of arteriosclerosis.

From the time of her admission and up until this point in her course gradual clinical improvement with moderate weight loss was noted. During the fourth week of her hospitalization she was started on a series of salt-poor albumin infusions. Overt signs of congestive heart failure developed and the infusions were discontinued. She began to complain of precordial pain. An electrocardiogram confirmed the presence of auricular fibrillation. Dyspnea and chest pain continued, and in spite of all supportive efforts the patient died thirty-three days after admission. Throughout her entire hospital course the patient remained afebrile with no significant fall in blood pressure or change in vital signs until shortly before her death.

The postmortem studies, gross and microscopic, corroborated the diagnosis of lupus erythematosus, with the following anatomic diagnoses: disseminated lupus erythematosus with especial involvement of blood vessels of the kidney, spleen, gastrointestinal tract, liver, pancreas, urinary bladder, skin, brain, etc.; old and recent focal hemorrhages and infarcts in cerebral cortex, basal ganglia, pons and cerebellum; anasarca; parathyroid hyperplasia, moderate; cardiac hypertrophy (480 gm.); primary tuberculous complex of lung with old

and recent disseminated tuberculosis involving abdominal lymph nodes and liver; hyperplasia of sternal marrow; small peripheral bronchial adenoma; surgical absence of appendix, tubes, ovaries and uterus; old fibrous peritoneal adhesions.

A prominent feature of the lupus erythematosus was the extreme fibrous thickenings about the splenic arterioles, so that these lesions were conspicuous grossly on cut surfaces of the spleen. (Fig. 4.)

Microscopic sections of kidney showed the wire-loop appearance in nearly every glomerulus and the capillaries were obliterated by the process in some of the glomeruli. Epithelial cells about the tufts were frequently increased in number. Regions of tubular atrophy and interstitial fibrosis occurred. Moderate arteriolosclerosis was noted.

COMMENTS

Nephropathy is an important clinical and pathologic findings in disseminated lupus erythematosus. The frequently associated skin lesion may be absent. Montgomery and McCreight found renal involvement in 100 per cent of their acute cases and in approximately 70 per cent of their subacute group. The latter incidence approximates that of other series. The clinical manifestations of renal involvement may be absent throughout the course of the disease or may precede other changes. They are thought to be the most frequent indication of visceral dissemination. The most common find-

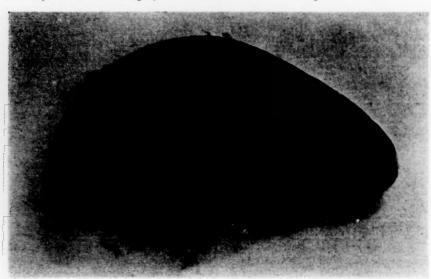


Fig. 4. Disseminated lupus erythematosus. Spleen showing periarterial fibrosis of the penicillary arteries, a lesion characteristic of the disease.

ings are those referable to the urine which at some time during the course of the disease will contain protein. 11,12 Proteinuria may predominate, with resulting nephrotic syndrome or variant thereof. The sediment may show red and white blood cells in varying amounts scattered or in casts as well as casts of other descriptions. Other evidence of functional impairment does not occur until the disease is advanced. Detailed pathologic features have been well described previously and therefore will not be discussed at this time. 13,14 However, it may be emphasized that distinct lesions are most apt to be found in the kidneys.

The nephropathy of disseminated lupus erythematosus in several aspects resembles that associated with diabetes mellitus. Their incidence seems to be increasing. In regard to diabetes this increase is probably due to prolonged life with the use of insulin. In lupus this increase may be associated with greater accuracy of diagnosis and an alteration in the natural course of the disease produced by the use of ACTH or cortisone. In the case presented, however, the patient did not receive such medication. The syndrome of true nephrosis is unusual in either of these conditions for there is usually some degree of hypertension and/or azotemia. Also, extreme hypercholesterolemia is rarely observed. Another similarity is seen pathologically since the definitive renal lesions of both diseases primarily involve the capillaries of the glomerular tufts and their basement membranes. The treatment of both diabetic and lupus nephropathies is frequently unrewarding. Our experience agrees with that of Heller and others in that steroids are of little or no benefit in such cases of disseminated lupus erythematosus.¹⁵

In regard to the technic of our renal biopsy procedure, suffice it to say that a modified Silverman needle is used through a posterior approach with the patient in the prone position. Some important contributions by the renal biopsy procedure as well as descriptions of technics have already been reported. 16-19

CONCLUSIONS

A case of disseminated lupus erythematosus is presented and discussed. The diagnosis was confirmed antemortem only by a renal needle biopsy. Thus the value of needle biopsies of the kidney in the diagnosis of diffuse renal disease is again demonstrated.

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Bilateral Renal Vein Thrombosis and the Nephrotic Syndrome*

Associated with Lesions of Polyarteritis Nodosa

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The syndrome of renal vein thrombosis in the infant is a well known entity. 1.2 It usually occurs in dehydrated infants suffering from severe diarrhea and is marked by hematuria with unilateral or bilateral renal enlargement. If prompt nephrectomy is not performed when the thrombosis is unilateral, shock and death follow shortly. In the adult renal vein thrombosis may also lead to infarction of the kidney. In some instances, however, renal infarction does not occur; and when the renal vein thrombosis is bilateral, an occasional case will present the complete clinical picture of the nephrotic syndrome.

In reviewing the literature we were able to find only four reported cases of bilateral renal vein thrombosis in which the nephrotic state characterized the course of the disease.⁴⁻⁷ Because of the very interesting nature of this syndrome, together with the paucity of reports concerning renal vein thrombosis as a possible etiology of nephrosis, we are reporting our observations in an additional case.

CASE REPORT

An eighteen year old white male entered a hospital on August 9th, complaining of cramping pain in the right lower quadrant of the abdomen, with nausea. He had been told that at the age of two years he had had edema and albuminuria for several months. After the edema cleared he remained well, and repeated urinalyses during childhood, adolescence and in the Army were normal. Physical examination on admission showed direct and rebound right lower quadrant tenderness. His temperature was 98.6°F. and the blood pressure 120/80. Urinalysis revealed three plus albuminuria with a

specific gravity of 1.030. The leukocyte count was 10,400 with a normal differential.

An appendectomy was performed and the appendix was normal upon pathologic examination. The patient made normal post-operative progress for seven days and then massive anasarca with periorbital, pretibial and sacral edema, ascites and left hydrothorax developed. These findings persisted throughout the remainder of his hospital course in spite of vigorous treatment with 50 to 100 gm. of serum albumin daily, infusions of plasma, a salt-free diet, bed rest and several injections of mercurial diuretics.

On August 31st, a diffuse area of cellulitis developed with red, tender induration of the skin and subcutaneous tissues of the right side of the body, extending from the lower costal margin to the mid-thigh anteriorly. Temperature rose to 103°F. and the white blood cell count to 29,100. Under penicillin therapy the induration of the skin and subcutaneous tissues slowly cleared by September 6th, at which time the patient developed generalized urticaria, apparently due to penicillin allergy. On September 16th the cellulitis recurred in the same area and was again controlled by penicillin. Urticaria again appeared but was relieved by the administration of epinephrine and pyribenzamine.® Expiratory wheezes were heard over the lung fields during this period and marked tenderness persisted over the right thigh from the knee to the inguinal

During the early days of this illness the serum non-protein nitrogen was 38 mg. per cent, serum cholesterol 565 mg. per cent, serum albumin 1.2 gm. per cent; the twenty-four-hour urinary excretion of protein was 26 gm. There was no anemia and the blood pressure remained

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Fig. 1. Coronal section of enlarged kidney. Multiple thrombi in renal veins are visible.

normal. Persistent moderate to marked albuminuria was present. The serum cholesterol rose to a peak of 860 mg. per cent in mid-September and declined somewhat thereafter. Pertinent laboratory findings are summarized in Table 1.

On October 16th the patient was transferred to Letterman Army Hospital. He appeared acutely ill and exhibited extreme anasarca. His blood pressure was 148/88, temperature 102.4°F. and pulse 75. The urine had a specific gravity of 1.006 and gave a four plus reaction for albumin. Microscopically, the urine showed many white blood cells and coarsely granular casts, as well as occasional hyaline casts and oval fat bodies. The hemoglobin was 15.9 gm. per cent, leukocyte count 23,360 with 94 per cent neutrophils.

Although the patient felt better and had several periods of diuresis following serum albumin injections, the general course was gradually downhill, with a progressive increase in anasarca. During the last three weeks of his hospitalization, while receiving 50 gm. of serum albumin daily, the patient had an average daily urinary excretion of 77 gm. albumin. On October 29th he had a sudden severe pain in the left chest, followed by dyspnea, shock and left-sided pleuritic pain. His temperature rose to 103.6°F. and the leukocyte count to 57,600. Signs and symptoms of thrombophlebitis of the veins of the left lower extremity and pelvis were noted. On heparin therapy the thrombophlebitis gradually cleared. Moderate anemia developed. On November 6th a pericardial friction rub was heard. Without

further apparent change in his condition he expired on November 11th, the ninety-fifth day after his initial hospitalization.

TABLE I SUMMARY OF LABORATORY DATA

		Hemo-			
Hospital Days	NPN (mg. %)	Cholesterol (mg. %)	Albumin (gm. %)	Globulin (gm. %)	g lobin (gm. %)
11	43				15.0
20	44	565			
28	46	640			14.8
33		750	1.2	2.1	16.0
40	50	860			
57	30	624	1.2	3.1	15.7
73	38	542	1.5	1.8	
83	35	460	1.6	2.0	14.4

Urinalyses

Hospital Days	Specific Gravity	Protein	Microscopic
1	1.030	3+	Occasional WBC
11	1.030	4+	Negative
21	1.028	2+	Occasional WBC; many granular casts
31	1.026	3+	3-5 RBC/HPF; many granular casts
45	1.020	3+	5-10 RBC/HPF; occasional granular and waxy casts
68	1.025	3+	Loaded with WBC
73		3+ 3+	1-3 RBC/HPF; 6-10 WBC/HPF; frequent oval fat bodies and granular casts; occasional hyaline cast

The pertinent autopsy findings were as follows. The body was pale and emaciated, the abdomen protuberant. There was pitting edema of the dependent parts. The abdominal cavity contained 2,500 cc. of clear fluid, the right

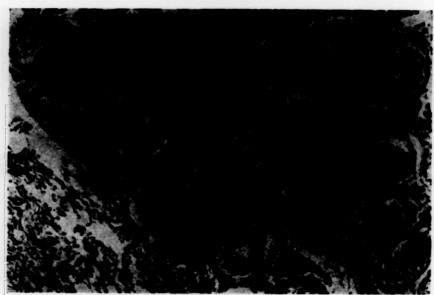


Fig. 2. Section of testis showing an acute necrotizing arterial lesion. Note the inflammatory exudate within the arterial wall.

pleural cavity 1,500 cc., the left pleural cavity 2,000 cc. and the pericardial cavity 125 cc. The lower lobes of both lungs were dark purple in color and on section the vessels were seen to contain many firm pinkish-tan thrombi. The heart and coronary vessels appeared normal. The spleen weighed 290 gm. and the liver 2,315 gm. Both kidneys were enlarged: the left weighed 390 gm., the right 295 gm. (Fig. 1.) The surfaces were smooth and generally white with a few areas of dark red mottling. The cortex of both kidneys was thickened and light tan in color. The medullae were normal. Both renal veins were filled with thrombi which had a granular surface and extended from the mouths of the renal veins into the renal substance beyond the arcuate veins. There were no thrombi present in the inferior vena cava or iliac veins. The veins of the lower extremities were not examined.

Microscopic examination of the heart showed widespread focal areas of degeneration of the myocardium with loss of myocardial fibers, increase in interstitial nuclei and the presence of macrophages, lymphocytes and mast cells. The major coronary arteries showed moderate intimal thickening, while the smaller radicles showed slight sclerosis. No definite evidence of arteritis was seen in multiple sections reviewed.

In the testicles the small arteries showed fibrinoid degeneration of the media with polymorphonuclear infiltration of the vessel wall and surrounding tissue. (Fig. 2.) Most of the small and medium-sized pulmonary arteries, especially

those to the lower lobes, contained partially or well organized thrombi. The liver showed distention of the central veins and sinusoids. One section showed inflammatory infiltration of the wall of a branch of the hepatic artery in Glisson's capsule. The pancreas showed occasional small foci of necrosis and one small artery showed fibrinoid degeneration of the muscular coat and perivascular round cell infiltration. Despite intensive search of multiple kidney sections no evidence of any glomerular abnormality was found. The capillary tufts were intact and a thin basement membrane was present. Bowman's capsule and the tubules contained pink staining fluid. Some tubules were packed with acute and chronic inflammatory cells in various stages of disintegration and most tubules were distended. The tubular epithelium was absent in places and various stages of degeneration and repair were observed in other areas. Focal and diffuse inflammatory cell infiltrates were present throughout the interstitial tissue. Almost all of the veins contained thrombi in various stages of organization. Those at the corticomedullary junction appeared older and were fibrosed. The renal arteries and arterioles showed no definite evidence of arteritis, although many of the arcuate arteries revealed a splitting and various degrees of disruption of the elastic lamellae.

The final anatomic diagnosis was: bilateral thrombosis of renal veins; nephrosis, severe; polyarteritis nodosa involving testes, pancreas and liver; myocarditis, focal, severe; pulmonary artery thromboses (embolic?), multiple, involving all lobes of both lungs; anasarca, moderate.

COMMENTS

In experiments performed on dogs Rowntree, Fitz and Geraghty8 showed that bilateral complete constriction of the renal veins (or unilateral renal vein constriction with the other kidney removed) could be produced gradually with maintenance of good renal function. Initially, the urine contained protein, red blood cells, hyaline and granular casts. After weeks or months the animals appeared in good health and renal function was normal, although mild albuminuria usually persisted. In explaining the lack of ill effects in the dog after renal vein obstruction, the authors emphasized the importance of the development of collateral venous channels from the kidneys. Marked enlargement of the capsular, ovarian, lumbar, adrenal and ureteral veins was observed.

Although the clinical diagnosis of renal vein thrombosis in adult man had been made a number of times previously, ⁹ Shattock ¹⁰ in 1913 first described a case in detail with postmortem findings. His patient had albuminuria which persisted for twenty-five years but at no time was there evidence of renal insufficiency or of the nephrotic syndrome. Autopsy revealed complete occlusion of the inferior vena cava from below the hepatic veins to and including the common iliac veins. The renal veins were occluded at their entrance to the inferior vena cava. A number of similar cases have been reported since.^{3,11}

In 1939 Derow and co-workers4 reported a patient with recurrent thrombophlebitis in whom the nephrotic syndrome was present for more than a year prior to death. Autopsy revealed almost complete occlusion of the entire inferior vena cava from the common iliac veins to a level just below the hepatic veins. Both renal veins were occluded from the inferior vena cava to the hilus of the kidney, and there was also occlusion of the portal, splenic, inferior mesenteric and superior mesenteric veins. Similarly, Fishberg⁵ observed a patient with migrating phlebitis who subsequently manifested the nephrotic syndrome for two years and who, at necropsy, showed a canalized thrombosis of the inferior vena cava and both renal veins. He observed that the nephrotic syndrome could be produced "in all its details by thrombosis of the renal veins." Bell⁶ and Allen⁷ have each described an additional case of the nephrotic

syndrome resulting from bilateral renal vein thrombosis.

In the patient we have presented (the fifth such case), the nephrotic syndrome with hypoalbuminemia, albuminuria, anasarca and hypercholesterolemia was observed for almost three months before the patient expired. Albuminuria was marked throughout the patient's illness but, in addition, occasional urine specimens contained some red blood cells, white blood cells, hyaline, granular and waxy casts. (Table 1.) These are essentially the same findings which were observed by Derow et al.4 The blood pressure was normal throughout the course of our patient's illness. Hypertension was previously noted only in the case reported by Bell.6 This is in keeping with the experimental observation that bilateral renal vein occlusion in the dog produces only transient hypertension in some animals and no blood pressure elevation in others, 12,13

At postmortem examination in our case we found thrombosis of both main renal veins extending into the renal parenchyma. (Fig. 1.) In addition, arterial lesions of polyarteritis nodosa were found. These were numerous in the testes (Fig. 2) but only a few isolated lesions were found elsewhere (liver capsule and pancreas). In the kidneys no evidence of active arteritis was found but many of the arcuate arteries showed splitting and disruption of the elastic lamellae. It is difficult to postulate what role these polyarteritic lesions played in the course of this patient's illness, although it is possible that renal venous wall involvement (none was actually demonstrated) may have been responsible for the renal vein thrombosis. The possibility also exists that the arterial lesions may have been a result of the patient's allergic response to the penicillin which was administered after the onset of the nephrotic syndrome. Similar arterial lesions were observed clinically and experimentally by Rich 14.15 after the administration of sulfonamides and they were considered to be manifestations of hypersensitivity. More recently Harkavy¹⁶ has noted the occurrence of necrotizing arterial lesions in some cases with penicillin sensitivity.

In the patient with thrombosis of the inferior vena cava and renal veins studied by Shattock, ¹⁰ it was postulated that the thrombosis may have arisen as a result of previous dissection within the venous wall (a counterpart to medial dissection of the aorta). This remains only supposition to

the present. It would appear more likely that such thrombosis is generally secondary to a thrombophlebitis although, admittedly, the origin or etiology of the thrombophlebitis may be unknown.

There does not appear to be any distinctive clinical pattern to the nephrotic syndrome occurring with renal vein thrombosis although the paucity of reports prevents any broad view of the subject. A grossly abnormal urinary sediment was present in our patient and in the other case4 in which detailed analyses were given. The clinical history is given in three of the cases previously reported. 4-6 In two of these patients there was clear-cut evidence of recurrent thrombophlebitis in the lower extremities. Although this condition was not noted in our case until after the onset of the nephrotic syndrome, it may have been present earlier but not detected. At the present time it would appear that the only way to make the diagnosis of bilateral renal vein thrombosis in a patient with the nephrotic syndrome with fair certainty antemortem, short of direct observation at surgery, would be by dye visualization of the inferior vena cava or the renal veins. The use of this method has not been reported.

SUMMARY

Bilateral renal vein thrombosis in the adult may produce the complete picture of the nephrotic syndrome. Such a case is reported together with a review of the literature. In addition to the renal vein thromboses, necropsy revealed necrotizing arterial lesions in several organs.

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Selective Sensitivity of the Purkinje Cells of the Cerebellum *

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THE selective sensitivity of particular elements of the neuraxis to both exogenous and endogenous influences, although little understood, is well recognized. Instances of preponderant damage to the substantia nigra by the virus of epidemic encephalitis, to the anterior horn cell by the virus of poliomyelitis, and to the basal ganglia by carbon monoxide, manganese or copper are well known. Evidence is accumulating that the reticular formation of the brain stem is particularly sensitive to ether and the barbiturates. While sufficiently intense exposure to most toxic agents will presumably affect many elements of the nervous system, it would seem that anatomic and chemical factors, which for the most part remain obscure, will tend to result in a predilection on the part of particular neural structures for particular agents. It is the purpose of this paper to call attention to yet another instance of relatively selective sensitivity on the part of an anatomic structure within the nervous system.

CASE REPORTS

CASE I. A twenty-two year old Air Force cadet was admitted to a military hospital on May 5, 1943. Twenty-five days before admission a purulent urethral discharge, from which gramnegative intracellular diplococci were smeared, developed. Treatment with both sulfathiazole and sulfadiazine did not affect the discharge however, and three weeks prior to admission he experienced the first of several attacks of right lower quadrant abdominal pain accompanied with nausea and relieved by vomiting. About the same time he noted several "lumps" in his right groin. On the day prior to admission he had a temperature of 102°F. Past and family histories were non-contributory. On physical examination the positive findings were mild tenderness to palpation in both the epigastrium and right lower abdominal quadrant, glands in

the right groin, and a thick yellow purulent urethral discharge. The neurologic examination was normal. Hemograms, serologic tests and urinalysis were within normal limits aside from ten to twelve pus cells per high power field in the urine.

Because of his failure to respond to sulfonamides on the third hospital day three intravenous injections (0.2, 0.2 and 0.15 cc.) of typhoid vaccine were administered at twohour intervals. Immediately after the third injection the patient "complained excessively loudly of precordial pain, became spastic and lapsed into unconsciousness." His axillary temperature at this time was recorded as 110°F. The pupils were small and the jaw held tightly shut. The tendon reflexes were everywhere brisk. The plantar responses were flexor. One hour later, despite prompt institution of measure to control his fever, the temperature was 108°F., the pulse 120 and irregular, and the blood pressure 80/0. Generalized seizures developed for which he was given sodium pentothal intravenously. Blood pressure remained depressed, pulse fast and irregular, and temperature elevated above 104°F. for the next twelve hours. Thereafter there was a gradual defervescence with occasional elevations to 105°F. On the third day the patient became icteric. A left pleural effusion was noted. One week later bronchopneumonia developed which gradually cleared. Thirty-five days after admission the temperature was normal.

One day after the injection of typhoid vaccine the red count dropped to 3.75 million and the hemoglobin to 50 per cent. Differential blood smear revealed 40 stab forms, 47 segmented polymorphs and 13 lymphocytes. The non-protein nitrogen on the following day was 83, urea nitrogen 28, chlorides 561 mg. per cent, and CO₂ combining power 29 vol. per cent. The icteric index rose to 19 on the third day and the

^{*} From the U. S. Veterans' Administration Hospital, New Orleans, La.

prothrombin time was 50 per cent of normal. The urine albumin was 2+ and many granular casts were noted on microscopic examination.

Treatment during the acute period consisted of measures to lower the temperature. The patient was placed in an oxygen tent and given whole blood and plasma transfusions. Six days following the onset he would protrude his tongue on command and would attempt to talk. He could not, however, make intelligible sounds. Four days later it was possible to remove him from the oxygen tent. He was noted to be agitated and restless and to sleep only for short intervals. His movements were described as choreo-athetoid in character. He could not grip with his left hand. Tendon reflexes were brisk and plantar responses flexor.

One month later he was described as emotionally labile. Most of the time he remained on his back with his arms flexed on his trunk. Passive movements were resisted. The athetoid movements had disappeared but the patient was too clumsy to feed himself, stand or walk. He could not talk intelligibly. Psychologic testing two months after the onset revealed a markedly dysarthric and emotionally labile individual who tended to perseverate. There was some motor aphasia.

Two months later he was transferred to a veterans' facility where he remained six months. A note at the time of his discharge describes the patient as being able to walk unassisted, feed and dress himself. There was a marked articulatory speech defect. His gait was considered to be spastic.

The patient was admitted to the Veterans' Administration Hospital, New Orleans, La., in September 1953 for re-evaluation of his physical status. On examination he proved to be a well developed and nourished young man. His speech was markedly dysarthric. He walked with a broad based, somewhat staggering and questionably spastic gait. On both heel to knee and finger to nose tests there was marked decomposition of movement. Past pointing was evident both with the eyes open and closed. Rapid alternating movements were poorly performed bilaterally. The tendon reflexes were hyperactive but symmetrical. Plantar reflexes were flexor, abdominal and cremasteric reflexes were active and symmetrical. Cranial nerves, sensation and intellectual function were unimpaired. Laboratory studies including electro-encephalogram, skull x-rays, serologic tests, hemograms and urinalysis were all within normal limits.

Comment. The presenting picture was one of marked cerebellar deficit. Two features, the rather spastic character of the gait and the brisk tendon reflexes, might represent more extensive involvement of the nervous system. In view, however, of the normal superficial reflexes and electro-encephalogram we are inclined to the opinion that the spasticity represents involvement of the anterior cerebellum.

Case II. A sixty-three year old man was admitted to the hospital November 12, 1952, with high fever and acute delirium. There was a history of sudden onset of hard shaking chills, profuse diaphoresis, high fever and cough productive of yellow sputum two days prior to admission. A high but unrecorded fever had persisted throughout the second day of illness. The patient became weak and listless, and on the morning of admission, was acutely delirious.

Physical examination revealed a well developed, slightly obese, elderly man who was acutely ill, dehydrated, mentally disoriented and in a state of agitated delirium. Temperature was 104°F. rectally, respirations 40 per minute, pulse 140 per minute, blood pressure 128/82. Respirations were short, rapid and with an expiratory grunt. There were medium and fine moist rales heard over the right upper lung field. A tender but soft and smooth liver was palpable three fingerbreadths below the right costal margin. The skin was hot and dry. Neurologic examination revealed a stuporous, acutely ill man with occasional periods of agitated delirium. He reacted only to painful stimuli. The deep tendon reflexes were generally hypoactive but equal, superficial reflexes could not be elicited; there was no paralysis or tremor.

Laboratory examination revealed a leukocytosis of 16,400 with 96 per cent neutrophils, 4+ albuminuria, blood urea nitrogen of 26 mg. per cent, plasma CO2 of 18.8 mEq./L., and serum chlorides of 90 mEq./L. Blood culture was negative. Sputum culture grew out rare colonies of Staphylococcus aureus, beta hemolytic streptococcus and alpha streptococcus, but was negative for pneumococci. Three sputum concentrates were negative for acid-fast bacilli. At the time of admission the serum bilirubin was 1.7 mg. per cent and there was BSP retention of 9 per cent at the end of forty-five minutes. Spinal fluid examination revealed clear colorless fluid under normal pressure. Complement fixation and colloidal gold tests were normal. A culture was sterile. Chest x-ray on admission revealed pneumonia of the basilar portion of the right upper lobe. X-rays of the skull were normal. Both electrocardiogram and electro-encephalogram were normal. Three sputum examinations for malignant cells were negative. Skin tests for tuberculin, coccidioidin and histoplasmin were negative.

The patient was treated with large doses of procaine penicillin, and with streptomycin 1 gm. daily. When the rectal temperature exceeded 105°F., intravenous fluids and electrolytes were administered and frequent alcohol sponges initiated.

During the first thirty-six hours the patient remained acutely ill, tachypneic and delirious with rectal temperatures ranging from 104 to 106°F. Thereafter and through the third and fourth hospital days, he gradually improved with decreased tachypnea and a fall in temperature from 102.4°F. rectally on the morning of the third hospital day to normal by the morning of the fifth hospital day. During this period his sensorium rapidly cleared. On the fourth hospital day it was noted that his speech was markedly slurred, garbled and rather explosive and staccato in quality. By the end of the first week he was recovered from his infection and was ambulatory; however, a persistent dysarthria, slight difficulty in swallowing with occasional regurgitation of liquid through the nose, impairment of use of the right hand and upper extremity for skilled movement, slight ataxia of both upper extremities with terminal tremor and overshooting on the past pointing test were noted. During the next eight weeks patient was given speech training but made little improvement. He was discharged from the hospital January 13, 1953. At that time x-ray of the chest revealed complete clearing of the pneumonic infiltration.

Follow-up examination six months later revealed marked slurring of speech, difficulty in swallowing with regurgitation of fluid through the nose, and ataxia of the upper extremities, more marked on the right. The remainder of the neurologic examination was normal. It was believed that there had been no essential change in the positive findings during the intervening six months.

REVIEW OF THE LITERATURE

The neurologic findings, ataxia, dysarthria and dysdiadokinesis suggest cerebellar disease. The freedom from involvement of other contiguous elements of the neuraxis suggests a parenchymatous process. Parenchymatous de-

generation of the cerebellum has been widely recognized since 1922 when Marie, Foix and Alajouanine8 reviewed the literature and reported five cases of progressive ataxia, dysarthria and dysdiadokinesis in elderly individuals. The average age of their patients was fifty-seven, with ages ranging between forty and seventy-six. By 1933 Parker and Kernohan9 were able to find reports of thirteen such cases in addition to one of their own. Aside from the relatively advanced ages of their patients neither Marie et al. nor Parker and Kernohan were able to detect any characteristics of this syndrome which might be of etiologic import. Those cases which came to autopsy showed marked involution of the Purkinje cells, particularly of the dorsal and lateral aspects of the cerebellum. There were minor, if any, changes elsewhere in the nervous system. Romano, Michael and Merritt 10 in 1940 published five similar cases. Their patients, none of whom were examined postmortem, all had long histories of chronic alcoholism. Marie et al. specifically excluded alcohol as an etiologic factor in four of their five cases.

The syndrome presented by our patients shows certain noteworthy differences from the parenchymatous cerebellar syndrome of late life. Most striking are the abrupt onset of symptoms following an episode of hyperpyrexia and the non-progressive course. Weisenberg 14 as early as 1912 reported an instance of non-progressive ataxia and dysarthria having its onset following sunstroke. He also refers to two cases described by Nonne. Similar cases have been published by Stewart¹² and Freeman and Dumoff.⁴ Their patients, thirty-two and thirty-eight years of age. respectively, had each experienced a sunstroke with coma and prolonged hyperpyrexia. Cerebellar signs including dysarthria, ataxia and dysdiadokinesis were noted on recovery from the acute episode. These had not changed during a follow-up period of several years in the case of Stewart's patient. McAlpine⁶ mentions without giving details three similar cases which he encountered among British troops in the Middle East and India. Two of these individuals recovered, the third had a persisting cerebellar syndrome. More recently Cruickshank 1 reported the same sequence of events in the course of acute rheumatism. The patient, a man of twenty years, experienced his first attack of rheumatic fever. His temperature at one point reached 110°F. by rectum. On recovery he presented a severe but not progressive cerebellar syndrome.

Silverman and Wilson¹¹ describe a similar complication in a woman of thirty-nine in whom hyperpyrexia developed with temperatures as high as 108.4°F., following thyroidectomy. One year postoperatively this woman was still institutionalized with crippling but non-progressive ataxia. Freedman and Schenthal3 reported two similar cases. One of their patients had at the time of examination been chairridden for twenty-five years following a systemic infection at age thirty-three. On examination she presented a severe cerebellar syndrome with trunkal ataxia as well as involvement of the extremities and marked dysarthria. After a period of improvement her condition had remained static for twenty-two years. Their second patient, a fifty-one year old ship's engineer, suffered heat stroke while on duty. A similar syndrome of dysarthria and dysdiadokinesis persisted eighteen months later.

None of these patients have come to autopsy. Freeman and Dumoff,4 however, examined the brain of a previously well man who died with hyperpyrexia following sunstroke. They noted marked reduction in the number together with alterations in the remaining Purkinje cells of the cerebellum. Malamud, Haymaker and Custer, 7 in an exhaustive study of the pathologic findings in heatstroke, made similar observations. They state that changes in the cerebellum were more striking, more consistent and more rapid in development than in any other part of the brain. The Purkinje cells were the earliest and the most severely damaged of all cellular elements. Except in cases of several days' survival the molecular and granular layers of the cerebellum showed only glial proliferation. Alterations of the cerebral hemisphere were later in development and less marked than those of the cerebellum.

OBSERVATIONS

It is evident from the foregoing that on a historical basis at least two parenchymatous cerebellar syndromes can be differentiated. Whether the syndrome of Romano, Michael and Merritt can justifiably be separated from that of Marie, Foix and Alajouanine is, we believe, an open question. Precisely the same sequence of events has been described in individuals both with and without a history of alcoholism. Table I summarizes the salient points of difference between what might be called progressive and non-progressive parenchymatous cerebellar disease.

The common feature presented by both syndromes is the selective development of ataxia, dysdiadokinesis and dysarthria together with a pathologic correlate—involution of the Purkinje cells. In neither syndrome is it apparent, however, why precisely this element of the neuraxis

TABLE I

	Progressive	Non-progressive
Age at onset	Average 57 (40-76)	Average 37 (20-63)
Nature of onset	Insidious	Abrupt
Antecedent illness	None (alcohol- ism in some cases)	Hyperpyrexia
Course	Progressive	Non-progressive; may be early improvement or recovery
Pathology	Cerebellar atrophy with involvement limited to Purkinje cells	No clinical case exam- ined; cases dying of hea- stroke showed predomi- nant involvement of Purkinje cells

should be principally involved. An explanation based on such anatomic considerations as the location of the Purkinje cells and their blood supply loses much of its force when it is considered that the involuted cells lie sandwiched between relatively intact molecular and granular layers. Similarly the possibility that anoxia, secondary either to the vascular changes of advanced age or to those associated with heatstroke, is the answer fails to take into account the demonstration 13 that the small pyramidal cells of the cerebral cortex are more susceptible to anoxia than are the Purkinje cells. One is left with the conclusion that on the basis of some as yet unidentified metabolic process the Purkinje cells may respond with greater sensitivity to both aging and hyperpyrexia than will other cellular elements of the nervous system. In this connection it is of interest that Brain, Daniel and Greenfield,2 have recently reported subcortical cerebellar degeneration in association with carcinoma. While other structures were involved in their patients, the most conspicuously damaged cells were those of Purkinje. It is their conclusion that the Purkinje cells are especially vulnerable to either extrinsic poisons or internal metabolic disturbances.

SUMMARY

A non-progressive parenchymatous cerebellar syndrome following abruptly upon an episode of hyperpyrexia is described. The relevant litera-

ture is reviewed and the syndrome is differentiated from progressive parenchymatous cerebellar degeneration. Evidence is presented indicating that both the progressive and nonprogressive syndromes are associated with involution of the Purkinje cells.

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Autonomic Nervous System Involvement in Diabetic Neuropathy*

With Emphasis upon Diarrhea As a Manifestation Thereof

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The literature in recent years has contained several references to the varied manifestations of diabetic neuropathy. However, with many physicians the classical view has persisted that the condition is limited to the peripheral nerves and is characterized by symptoms of peripheral neuritis. It is not well known that autonomic nervous system disturbances due to diabetic neuropathy can involve the gastrointestinal tract, the genitourinary system and the peripheral autonomic nerve fibers.¹

The author recently encountered an interesting patient with diabetic neuropathy in whom diarrhea was the presenting complaint. Evidence of peripheral neuritis was initially so meager that the correct diagnosis was not suspected. It is hoped that the case report which follows will stimulate interest in the subject and lead to the correct diagnosis in certain cases presenting puzzling diarrheas of unknown etiology.

CASE REPORT

J. H., No. 48–686, was a forty-seven year old white male who entered the Thayer Veterans Administration Hospital, Nashville, Tennessee, on December 30, 1953, with a complaint of diarrhea of five months' duration. He had had diabetes mellitus for six years, had been admitted to this hospital several times with acidosis but had never been in coma. He was taking 35 units of NPH insulin and 15 units of regular insulin daily.

In August, 1953, five months prior to admission, the patient noted onset of diarrhea consisting of five to fifteen brownish-yellow, watery stools a day. Between episodes of diarrhea the

bowel movements were normal. Nocturnal fecal incontinence was a frequent complaint. After meals there was a tendency to have one to three bowel movements, these usually associated with "rolling and tumbling inside." There had been no blood observed in the stools nor were there any significant facts in the past history relating to the gastrointestinal tract.

Three months following the onset of these symptoms the patient was admitted to this hospital suffering from severe diarrhea, polyuria, polydypsia and weakness. He had lost 16 pounds in weight. Pertinent physical findings included absent ankle jerks, barely elicitable knee jerks and muscular tenderness and wasting. Laboratory data were as follows: Blood sugar 465 mg. per cent; carbon dioxide combining power 25.9 mEq./L.; five stools negative for blood, ova and parasites while a sixth showed a trace of occult blood; barium enema, negative. Although rigid control of the diabetes was not attained, the diarrhea cleared spontaneously and the patient was discharged.

An exacerbation of diarrhea occurred after three weeks and did not respond to paregoric. He was re-admitted on December 30, 1953, at which time the following history suggestive of diabetic neuropathy was obtained: About one month prior to the onset of the first attack of diarrhea complete loss of potency had occurred although libido had remained strong. There were no other genitourinary complaints. During this period he noticed the onset of sharp pains, numbness and sensations of cold in the lower extremities. At times the plantar surfaces of the feet were quite painful. For several months he had experienced swelling of the feet which

^{*} From the Medical Service, Thayer Veterans Administration Hospital, Nashville, Tenn. Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

required him to unlace his shoes after periods of standing.

Physical examination revealed an emaciated male appearing chronically ill and weak. Blood pressure was 80/60; pulse, 100. The skin was dry and loose. Pupils were small and reacted slowly to light. There was no evidence of diabetic retinopathy. Liver dullness extended 4 cm. below the right costal margin but the liver could not be palpated. Generalized weakness was present without localizing signs. The muscles were hypotonic with good coordination. Deep tendon reflexes in the arms were diminished; the knee jerks were obtained only with reinforcement. Ankle jerks were absent. Plantar stimulation gave equivocal Babinski signs. Superficial reflexes were intact. Bilateral stocking and glove hypesthesia to pain and light touch extended proximally to the knees and wrists. There was slight impairment of vibratory sensation in the ankles but position sense was normal.

Pertinent laboratory data follows: Urinalysis—sugar, four-plus; acetone, four-plus. Blood sugar—216 mg. per cent. Carbon dioxide combining power—21 mEq./L. Numerous stool examinations and cultures, negative. Spinal fluid, negative. Stool quantitative fat determination, normal. Roentgenologic studies of the colon, upper gastrointestinal tract and the small bowel were considered normal. Sigmoidoscopy showed no abnormal findings.

Because of a history of reduced sweating, a sweat test with iodine and starch was done. This revealed scattered and irregular areas of diminished and absent sweating which was most marked over the distal portions of the extremities.

About one month after admission the patient experienced an attack of agonizing continuous pain in each leg below the knee. The calf muscles were exquisitely tender and the skin was hyperesthetic with burning sensations. These were the first subjective symptoms of peripheral neuritis observed during his stay in the hospital and required demerol® for relief. Attacks of somewhat lessened severity continued to occur at frequent intervals.

Treatment was directed toward rigid control of the diabetes. Insulin dosage was increased to 70 units NPH insulin and 30 units regular insulin. Although a high calorie, low residue diet was prescribed, normal weight was not regained; and only partial relief of diarrhea occurred. Various therapeutic agents were administered, including atropine, crude liver

extract, vitamin B₁₂, pregnant mammalian liver extract (biohepulin) and BAL (British anti-lewisite). With the exception of BAL none of them caused any significant effect. Considerable improvement in the peripheral neuritis as well as the diarrhea was noted during administration of BAL. At the time of discharge, however, the patient continued to have intermittent bouts of diarrhea, and the symptoms of peripheral neuritis involving the lower extremities were still troublesome on some days.

Comment. This case of diabetic neuropathy is of interest because diarrhea was the presenting complaint. The usual symptoms of peripheral neuritis were not sufficiently troublesome to cause the patient to mention them spontaneously, although evidence to suggest their presence was obtained by direct questioning. Serious peripheral neuritis did develop, however, during his stay in the hospital. Since this complication is not unusual following the institution of insulin therapy in previously untreated diabetics, 1 it seems possible that the appearance of severe neuritis symptoms in this patient resulted from the vigorous treatment of the diabetes with considerable increases in insulin dosage. Although the patient's course was characterized by transient spontaneous remissions, definite over-all improvement was noted after institution of treatment with BAL.

MANIFESTATIONS OF AUTONOMIC DYSFUNCTION IN DIABETIC NEUROPATHY

Gastrointestinal. One of the most complete accounts of autonomic involvement in diabetic neuropathy is found in Rundles' article1 in which he reviews 125 cases of all types. Complaints referable to the gastrointestinal tract were no more common in diabetics without neuropathy than in non-diabetics. In diabetic neuropathy, however, severe constipation occurring as a change of bowel habit associated with the onset of neuritic symptoms was the most common abnormality noted and occurred in 42 per cent of his cases. Diarrhea was the second most frequent complaint and was seen in twenty-seven cases (22 per cent). In eleven of these diarrhea alternated with constipation; six patients had recurrent episodes of diarrhea; ten had continuous diarrhea. The diarrhea was often nocturnal in character, with fecal incontinence frequently noted. Meals were often followed by gaseous distention, borborygmi and urgent passage of two to four stools. Such stools were

usually liquid, light-colored and foul smelling. Examination of feces showed no excess fat, parasites or undigested food particles. Nausea, vomiting and abdominal pain were relatively uncommon, especially in patients with diarrhea. Roentgenologic studies showed frequent instances of disturbed intestinal motility with puddling and scattering of barium. 1.6 Patients with nausea and vomiting had prolonged gastric emptying.

The intermittent character of "diabetic nocturnal diarrhea" has been stressed by Sheridan and Bailey. Nocturnal fecal incontinence was found by them in thirty-one of fifty cases. No mention was made of the daytime occurrence of bowel movements. Peripheral neuritis was observed in twenty-two of forty cases and elevation of spinal fluid protein in seventeen of eighteen cases in which spinal fluid examinations were performed. In contrast to the findings of Rundles and his associates, upper gastrointestinal x-rays in seventeen cases were normal.

The clinical picture described by Rundles and by Sheridan and Bailey was confirmed in a recent review by Martin³ in which he studied 150 cases of diabetic neuropathy. Recurrent episodes of diarrhea occurred in 18 per cent. Investigations included sigmoidoscopy, barium enema and stool fat determinations; all were within normal limits. Half of his patients recovered when good control of diabetes was established but the remainder did not improve despite this.

Further reports are encountered in the literature describing the diarrhea of diabetic neuropathy. 4-12.16 However, in most of these it is mentioned briefly with little or no detailed account of clinical characteristics.

Genitourinary. Bladder distention was found in 14 per cent of Rundles' cases. Impotency, hesitancy, weakness of the urinary stream and acute retention sometimes preceded other symptoms of diabetic neuropathy. Martin found similar difficulties in 8 per cent of his cases. Cystometric examination in each series revealed an impaired or absent sense of bladder filling, low expulsive force and increased bladder capacity. Other patients have been reported, 12,13 one of whom responded well to control of the diabetes plus administration of prostigmin and mecholyl.

Peripheral Autonomic Nerve Involvement. Dependent edema not explainable on a cardiac, renal or hypoproteinemic basis was recorded in 28 per cent of Rundles' cases. He attributed it to involvement of the peripheral nerves of the autonomic nervous system. Other symptoms included trophic skin changes, perforating skin ulcers, decreased sweating, loss of pilomotor control and orthostatic hypotension. Martin^{3,14} found similar changes and described tests which demonstrated paralysis of sudomotor and vasoconstrictor fibers in 50 per cent of those tested. The remaining patients showed results similar to those seen after complete denervation of an extremity.

PATHOLOGIC FINDINGS

There is a dearth of material in the English literature concerning the pathology of the autonomic nervous system in diabetic neuropathy. Necrosis of scattered nerve bundles and the presence of arteriosclerosis of the endoneural and perineural vessels was described by Woltman and Wilder. 15 Little correlation was noted between clinical symptoms and the degree of arteriosclerosis. In biopsy specimens Martin¹⁴ thought the primary lesion was loss of axis cylinders with demyelination occurring as a secondary change. Loss of non-myelinated autonomic fibers was thought to exceed the loss of the large myelinated fibers. Postmortem examination in two of Rundles' cases1 revealed degeneration of the nerve trunks to the esophageal and celiac ganglia.

ETIOLOGY AND PATHOGENESIS

The few pathologic studies which have been performed provide a ready argument that diabetic neuropathy results from deficient blood supply. However, such an argument does not explain the occurrence of neuropathy in patients without evidence of sclerosis nor does it explain the rapid recovery seen in some cases. Martin's studies with skin temperature and oscillometric data argue against a vascular disorder as the etiologic agent.

Rudy and Epstein¹⁷ concluded from their studies that deficiency of vitamin B-complex was the cause of the condition. However, by their own admission 27 of 100 cases had adequate nutritional intake, thus suggesting either faulty digestion and absorption or some other factor. Investigations of pyruvate metabolism designed to measure deficiency of thiamine have been negative in diabetic neuropathy.³

Modern concepts of carbohydrate metabolism provide another theory of pathogenesis. It is well

known that nerve tissue depends in great part on carbohydrate for energy.18 The diabetic, by reason of insulin lack, is unable to utilize carbohydrate to the degree required for his metabolic needs and thus falls back upon fat for his energy requirements. 19 Since lipids form no small part of the substance of nerves, the metabolic disorder in diabetes mellitus could result in depletion of lipid content of nerve tissue. A suggestive chemical confirmation of this theory has been provided.20,21 Analysis of diabetic and non-diabetic nerves for cholesterol, phospholipid and cerebroside showed a decrease in lipid content of diabetic nerves. The degree of abnormality increased as the clinical symptoms increased, and poor control of the diabetes apparently intensified the abnormality.

From the data cited it seems possible that the pathologic change in the nerves of diabetic patients may result from two metabolic disturbances. First, the nutritional requirements of the nerves are insufficiently supplied because of primary insulin deficiency which results in inadequate carbohydrate utilization. Second, the use of body fats to supply the caloric requirements of the body may result in removal of lipids from nerve tissue. Secondary factors such as arteriosclerosis and vitamin deficiency may contribute to the damage which occurs in the nerve but they do not explain all the manifestations of the disease.

TREATMENT

In the treatment of diabetic neuropathy all authors agree that strict control of the diabetes is essential. Special effort should be made to maintain approximately normal blood sugar content. Caloric intake should be adequate to obtain a return to normal weight. This usually requires more calories than the average diabetic diet provides, and increased dosage of insulin is necessary in such cases. With such therapy, recovery usually occurs to some extent.⁵

Efforts directed at discovery of some specific therapeutic agent have yielded interesting results. Bargen, Bollman and Kepler²² used pancreatic juice without beneficial effect. Sheridan and Bailey² obtained good results in forty cases of diarrhea when treatment consisted of crude liver extract. However, Marble,²³ reporting two years later from the same clinic, states that only two of those forty cases had prolonged remissions or possible cures. Two recent encouraging reports^{9,10} describe the use of preg-

nant mammalian liver extract (biohepulin) with improvement in 80 to 90 per cent of two series of cases. Schneider²⁴ obtained improvement in twelve of twenty-two patients in whom BAL (British anti-lewisite) was used. All these reports await confirmation. Crude liver extract, pregnant mammalian liver extract, vitamin B₁₂ and atropine were used in the case reported without benefit. Partial relief of the peripheral neuritis as well as a decrease in diarrhea was noted following administration of BAL.

SUMMARY

1. Autonomic nervous system involvement in diabetic neuropathy is frequently overlooked. Symptoms may be related to the gastrointestinal tract, the genitourinary system or the peripheral nerves and include constipation, diarrhea, bladder retention, impotency and trophic changes in the extremities.

2. A case is presented of a diabetic in whom diarrhea was thought to be due to autonomic nervous system involvement.

Recent evidence suggests that the neuropathy may be due to metabolic defects associated with the diabetes.

4. Treatment should be directed toward control of the diabetes. Various agents are being investigated in an effort to discover a specific therapeutic agent. In the case reported the use of BAL was followed by some improvement. Crude liver extract, pregnant mammalian liver extract and other substances gave no relief.

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Solitary ('Monotropic') Thyrotropin Deficiency with Secondary Hypothyroidism*

Observations on Response to Thyrotropin, Growth Hormone and Sodium L-Thyroxin

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LTHOUGH incomplete or partial deficiency of anterior pituitary hormones is well recognized, there have been only a few reported instances of solitary or 'monotropic' deficiency of anterior pituitary hormones. Deficiency of this type limited to the thyrotropic hormone has been described only once previously to our knowledge.¹ It is our purpose to report herein an additional case in which certain other unusual features were present.

CASE REPORT

The patient, a twenty-seven year old white male student, was first seen by us in March, 1952. In 1944 while in the Navy he developed symptoms which led to the diagnosis of questionable duodenal ulcer. In the spring of 1949 he lost 25 pounds in three months on a high protein, low calorie diet which was prescribed because of obesity. Soon afterward low grade fever appeared. He was studied in our hospital in the summer of 1949 and a diagnosis of possible infectious mononucleosis was made. In late 1949 after subsidence of the fever, chronic malaise persisted.

Early in 1950 a group of symptoms appeared and recurred intermittently. These included the following: weakness, mental lassitude, drowsiness, intolerance to cold, polyuria, polydipsia, polyphagia, a sweet odor on the breath, craving for salt, air hunger, dyspnea on exertion, sharp pains in the mid-anterior chest, difficulty in focusing vision and fronto-orbital headaches. Faintness, sweating and nervousness often appeared after several hours' fasting and were relieved by food. From 1950 to 1952 the patient

was under considerable emotional stress. His symptoms progressed in severity and finally became constant. During this time he regained about 20 pounds. There was no loss of libido. In February, 1952, he was referred to our clinic from the Student Health Service of the University of Pennsylvania.

The patient was 5 feet 11 inches tall and weighed 214 pounds. He was well developed and slightly obese with symmetrical distribution of body fat. No stigmata of subcutaneous myxedema were present. He was somewhat dejected, listless and yawned frequently. His breath had an acetone-like odor. The skin was slightly yellowish, dry and warm; the hair was dry and brittle but not sparse. His thyroid was not palpable. Pulse rate was 80 and rhythm regular; blood pressure was 122/80. The genitalia and secondary sexual characteristics were normal. Examination was otherwise negative.

The following laboratory studies were normal or negative: routine blood counts and urinalyses; fasting and postprandial blood sugar levels; serologic test for syphilis; serum sodium, potassium, chloride, calcium, phosphorus and carbon dioxide content; liver function tests (bromsulfalein retention, cephalin cholesterol flocculation, thymol turbidity, total serum protein and A/G ratio); renal function tests (blood urea nitrogen, twelve-hour concentration test and urea clearance); roentgen studies of the skull and chest; and electrocardiogram, electroencephalogram and visual fields. Fluid intake and urine volume were not excessive.

Fasting eosinophil counts initially and during the periods of observation ranged from 44 to

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Solitary Thyrotropin Deficiency-Sampson et al.

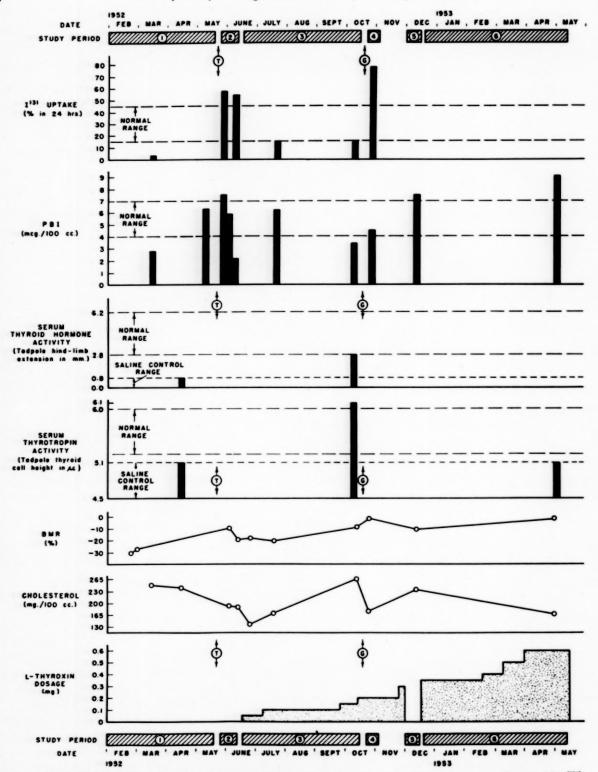


Fig. 1. Tests of thyroid function in relation to periods of special study, including responses to thyrotropin (T), growth hormone contaminated with thyrotropin (G) and L-thyroxin.

113 cells per cu. mm. In two tests the eosinophils responded to ACTH administration with respective falls of 46 per cent and 70 per cent at the end of four hours. The Kepler-Power-Robinson water excretion test was normal. The results of other pertinent studies during the periods of

SPECIAL STUDIES AND CLINICAL COURSE

Thyrotropin Administration (Study Period No. 2). In order to test the presence of thyrotropin deficiency various studies were made of the response of the patient's thyroid function to exogenous thyrotropin. In late May, 1952, lyophilized beef

TABLE I
URINARY HORMONE EXCRETIONS IN VARIOUS STUDY PERIODS

Study Period	1	2	3	4	5	6	1	
	Before Therapy	After Thyrotropin	After I-Thyroxin	After Growth Hormone	No Therapy	After !-Thyroxin	Normal	
Urinary Gonadotropin † (mouse u. per 24 hrs.)	> 48 and < 96	> 24 and < 48	> 8 and < 24	> 48 and < 95		> 24 and < 48	0 - 48	
Urinary Neutral 17 Ketosteroids † (mg. per 24 hrs.)	24.4 27.3	26.6	23.1 34.6	25.5 29.5 30.9	29 5	26.2	7.5 - 26	
Urinary Corticoids \$ (mg. per 24 hrs.)	6.7	6 05	3.7 4 8	3.5 4.4 4.2	2.6	5.2	2.5 - 4.5	
Urinary Estrogen ‡ (mouse u. per 24 hrs.)			> 67 and < 133	> 27 and < 44		< 13	0 - 27	

† Alcohol precipitation method; mouse uterine weight technic.

‡ Extraction after acid hydrolysis. In the case of urinary estrogen, extraction after acid hydrolysis; vaginal smear technic.

observation are shown in Figure 1 and Tables 1 and 11.

The initial measurements of basal metabolic rate (BMR), serum cholesterol, serum protein-bound iodine (PBI) and twenty-four-hour thyroid uptake of I¹³¹ indicated thyroid deficiency. (Fig. 1.) This evidence was supported by the absence of detectable thyroid hormone and thyrotropin activities in the serum with the stasis-tadpole method of D'Angelo and Gordon.² These findings were compatible with the diagnosis of hypothyroidism secondary to thyrotropin deficiency.³

Adrenocortical function was normal as measured by the pertinent tests listed previously and by those in Table I. Tests for gonadrotropic activity and gonadal function were likewise normal. The significance of the abnormal insulin sensitivity and hypoglycemia unresponsiveness shown in Table II will be discussed.

thyrotropin was administered intramuscularly in dosage of 30 mg. daily for three days. As can be noted in Figure 1 the BMR became normal and serum cholesterol decreased. The serum PBI rose slightly to a level of 7.6 µg./100 cc. The most marked response was in the uptake by the thyroid of a tracer dose (25 microcuries) of I¹³¹, which increased from 3 per cent in twenty-four hours to 57 per cent in twenty-four hours. The administration of thyrotropin was followed by nausea and temporary exaggeration of previous symptoms. About three days after the last injection these symptoms began to diminish. The patient then showed marked symptomatic improvement which lasted about ten days. Thereafter all symptoms quickly returned.

A similar response in thyroid function also followed administration of a crystalline growth hormone preparation that was contaminated with considerable thyrotropin (v. seq.). On the

basis of these responses to thyrotropin it was concluded that the patient was suffering from hypothyroidism of pituitary origin.

In response of the patient's thyroid function to thyrotropin, a dissociation was noted between changes in serum PBI and twenty-fourdaily (corresponding approximately to $1\frac{1}{2}$ gr. of desiccated thyroid). Incomplete symptomatic improvement followed this therapy. During this four-month period of therapy the BMR rose from minus 19 to minus 9 per cent. Fluctuation in the PBI levels occurred during this period.

TABLE II
TESTS OF GLUCOSE AND INSULIN RESPONSES IN VARIOUS STUDY PERIODS AS COMPARED WITH
THE NORMAL

Study Period	1	2	3	4	6			
	Before Therapy	After Thyrotropin	After I-Thyroxin	After Growth Hormone	After I-Thyroxin	Normal		
Fasting Blood Sugar (mg./100 cc.)	87	89	104	81	90	70 - 100		
Oral Glucose Tolerance (mg./100 cc.)	F 75 30' 85 60' 65 120' 68				80 119 - 88 84	After glucose, highest blood sugar level is 30-60 mg./100 cc. greater than fasting level.		
Maximum fall in blood sugar after insulin. (% of fasting value).	•	27%	† 34°C	26%	20%	30-55% of fasting value		
Maximum rise in blood sugar after glucose. (% of fasting value).	100%	134%	+113°C	116%	105%	125-175% of fasting value		

^{*} Severe symptoms of hypoglycemia; blood not drawn.

hour thyroid uptake of I¹³¹. Spontaneous fluctuation in the serum concentration of protein-bound iodine is suggested by the difference in values noted prior to the administration of thyrotropin. (Fig. 1.) During the first week after administration of thyrotropin the PBI level rose to slightly above the upper limit of normal; in contrast, the I¹³¹ uptake rose to a definitely hyperthyroid level. Three weeks following administration of thyrotropin, the PBI had fallen to a hypothyroid level, whereas the I¹³¹ uptake remained in a hyperthyroid range.

L-Thyroxin Therapy (Study Period No. 3). In June, 1952, sodium L-thyroxin therapy was started with an initial oral dose of 0.05 mg. per day. This dosage was gradually increased between June and October, 1952, to 0.15 mg.

(Fig. 1.) Low normal values for twenty-four-hour thyroid uptake of I¹³¹ were found in July and early October, 1952: 15 per cent and 14 per cent, respectively; both were higher than that found before treatment.

A second assay for thyrotropin and thyroid hormone activity in the serum made in early October, 1952, showed a rise in both values. The possible significance of this rise will be discussed.

Glucose and Insulin Tolerance Tests. Initial abnormalities were found in these tests. (Table II.) The standard oral glucose tolerance test showed a flat response. The intravenous glucose tolerance test, however, showed a brief rise in blood sugar at fifteen minutes to 50 mg. per cent above the fasting level and a rapid drop to normal thereafter; this was considered to be

[†] Average of two determinations.

within normal limits. This test was carried out for six hours without development of hypoglycemia or unusual symptoms.

An insulin tolerance test was performed, using the technic of Fraser, Albright and Smith.4 With this test, thirty minutes after the intravenous injection of 0.1 unit insulin per kilogram of body weight the blood sugar should normally fall to about 50 per cent of the fasting level; the fasting level should be reattained in 90 to 120 minutes. Only one-half the usual dose of insulin was used in our patient as a precaution in case of panhypopituitarism. The patient showed abnormal insulin sensitivity with a drop in blood sugar to 27 mg. per 100 cc., or 34 per cent of the fasting value and with symptoms similar to those originally presented. However, in contrast to the insulin-glucose tolerance test there was no evidence of hypoglycemia unresponsiveness.

The insulin-glucose tolerance test⁵ is based on the observation that the rise of blood sugar following an oral dose of glucose given thirty minutes after the intravenous injection of a standard dose of insulin is greater than that occurring after the oral administration of the same dose of glucose without insulin. Normally the blood sugar should fall to 45 per cent (range 30 to 55 per cent) of the fasting level thirty minutes after the intravenous injection of 0.1 unit insulin per kilogram of body weight. A fall greater than this indicates abnormal insulin sensitivity. Normally there should also occur a rise in blood sugar to 150 per cent (range 125 to 175 per cent) of the initial fasting level, sixty minutes after the oral ingestion of 0.8 gm. of glucose per kilogram of body weight, following the intravenous administration of insulin. Failure to attain this level is defined as hypoglycemia unresponsiveness. (Table II.) In this test repeated in various study periods, our patient showed slight insulin sensitivity and hypoglycemia unresponsiveness.

Administration of Growth Hormone Contaminated with Thyrotropin (Study Period No. 4). Additional studies were carried out during and after the administration of a growth hormone preparation in an effort to determine whether an intrinsic deficiency of adenohypophyseal growth hormone or of a related insulin antagonizing factor might be responsible for the patient's abnormal responses to insulin. In October, 1952, he received intramuscularly a preparation of lyophilized bovine growth hormone, 200 mg. daily for four days. The dose represented 2 mg.

of growth hormone per kg. per day. This preparation was contaminated with a high thyrotropin content, so that approximately 90 mg. of thyrotropin was received daily. Thus the total amount of thyrotropin given in study period No. 4 was about four times that given previously in study period No. 2. L-thyroxin was continued in dosage of 0.2 mg. daily during the administration of growth hormone.

Responses of the patient's thyroid function are shown in Figure 1 and some of the other responses are shown in Tables 1 and 11. Responses may be summarized as follows: (1) On the third day of growth hormone administration fever up to 101°F. appeared and persisted for twenty-four hours. With the onset of fever the following also appeared: malaise, nausea, sweet odor on the breath and strong ammonia or asparagus-like odor of the urine. These lasted for several days. Soon after this reaction subsided symptomatic improvement for several days was noted. (2) Significant glycosuria occurred on each day of administration of the growth hormone preparation despite the absence on these days of fasting or postprandial hyperglycemia or of change during this period in degrees of insulin sensitivity and hypoglycemia unresponsiveness. The glycosuria ranged between 2.6 gm. and 4.7 gm. in twenty-four hours. (3) A 5 pound weight loss occurred. (4) No significant changes occurred in the following values: blood urea nitrogen, twenty-four-hour urine volume, urinary excretion of creatinine, urinary excretion of gonadotropins, neutral 17-ketosteroids, corticoids or estrogens. There was no acetonuria. (5) The following responses as well as the symptomatic improvement noted were probably due to action of the thyrotropin content of the preparation: a slight rise in BMR and serum PBI, a marked rise in thyroid uptake of I131 and a significant decrease in serum cholesterol. These responses confirmed the previous evidence of primary thyrotropin deficiency and again demonstrated the dissociation of responses to exogenous thyrotropin between the serum PBI and the thyroid uptake of I131.

Twenty-Four-Hour Fast. In late October, 1952, several days after the last dose of growth hormone, the patient was fasted for twenty-four hours, meanwhile continuing to take L-thyroxin in doses of 0.2 mg. daily. At the end of this fast there was no development of hypoglycemia or of any symptoms suggestive of panhypopituitarism or adrenocortical deficiency.

Additional Observations. From mid-October to late November, 1952, the patient continued to take L-thyroxin in dosage of 0.2 mg. daily. In November he complained of late afternoon fatigue; this was not relieved by food. When he was extremely tired he would occasionally notice a transient sweet odor on his breath. Apart from these none of the other original symptoms was present. On November 27th, the daily dose of

L-thyroxin was increased to 0.3 mg.

Discontinuation of L-Thyroxin (Study Period No. 5). On November 30, 1952, L-thyroxin was discontinued. About ten days later drowsiness, frontal headaches, sensation of air-hunger and sweet, acetone-like odor on the breath reappeared. At this time a test for plasma acetone was weakly positive, without glycosuria or ketonuria. Concomitantly, serum CO2, blood urea nitrogen, fasting blood sugar and concentrations of serum and urinary organic acids showed normal values.

During this period the response of blood glucose to epinephrine was determined following an overnight fast, using the technic of Cantarow and Trumper.6 There was a marked rise in blood sugar following epinephrine, representing a normal response. There was some decline in BMR and a rise in serum cholesterol in December, 1952, about two weeks after the withdrawal of L-thyroxin. The serum PBI was high normal at this time, probably as a result of previous L-thyroxin therapy.

Resumption of L-Thyroxin and Subsequent Course (Study Period No. 6). On December 14, 1952, Lthyroxin therapy was resumed in dosage of 0.35 mg. daily. Following this the symptoms that had recurred after the withdrawal of L-thyroxin disappeared or diminished; however, undue fatigability persisted. Therefore, beginning on February 17, 1953, the daily dose of L-thyroxin was increased gradually until a maximum of 0.7 mg. (corresponding approximately to 7 gr. of desiccated thyroid) was attained in July, 1953. At the same time caloric intake was somewhat restricted.

In April and May, 1953, when the daily dose of L-thyroxin was 0.6 mg., the BMR and serum cholesterol were normal whereas serum PBI was above normal. In May, 1953, serum assay revealed no thyrotropin activity, similar to the assay before treatment but in contrast to the high activity noted in October, 1952, when the dosage of L-thyroxin was only 0.15 mg. daily.

An oral glucose tolerance test done at this

time showed a normal peak at thirty minutes, in contrast to the originally flat curve. (Table 11.) An insulin-glucose tolerance test at this time showed no significant change in the previously noted slight abnormalities of insulin sensitivity and hypoglycemia unresponsiveness. (Table 11.) There was no further change in the urinary excretion of 17-ketosteroids or corticoids.

With the increase in dosage of L-thyroxin there was a parallel clinical improvement so that by July, 1953, the patient felt well, although he still required nine to ten hours of sleep nightly. With the larger doses of L-thyroxin the sweet odor did not reappear on the breath and no acetone was detectable in the plasma. Between February and July, 1953, he lost approximately 18 pounds; his weight in July, 1953, was 204 pounds.

COMMENTS

Cases of incomplete failure of adenohypophyseal function involving various groups of hormones are well recognized.7.8 However, there have been only a few reports of solitary ('monotropic') deficiency of adenohypophyseal hormones. Examples which can be cited include interstitial cell stimulating hormone deficiency in cases of eunuchoidism with fertility, 9 and possible isolated deficiency of adrenocorticotropin.1

In the previous description by Shuman¹ of solitary thyrotropin deficiency with secondary hypothyroidism the patient was a severely diabetic, psychotic sixty-four year old Negress with hypertension and retinopathy in whom the adrenocortical responses and follicle-stimulating hormone excretion were normal. The administration of thyrotropin demonstrated the presence of a physiologically intact and responsive thyroid gland. The diagnosis of myxedema in this patient was first made on clinical grounds. Desiccated thyroid therapy was instituted and the dose was gradually increased to 4 gr. daily. The clinical response was reported in these terms: there was no change noted in the mental state of the patient, and during the period of increasing thyroid dosage there was gradual decrease of the insulin requirement from approximately 120 to 40 units daily. Improvement in the hypothyroid symptoms was not mentioned.

Our patient showed clear evidence of hypothyroidism, the secondary character of which was indicated by the initial absence of detectable thyrotropin in the serum by the stasis-tadpole test³ and by the response to exogenous thyrotropin. 10,11 The absence of classical myxedema and the relatively slight degree of hypercholesterolemia are compatible with pituitary hypothyroidism. There was no evidence of adrenocortical or gonadal deficiency, indicating the solitary nature of the thyrotropin deficiency. The rather consistent maintenance of neutral 17-ketosteroid excretion at top normal levels or above, the intermittent elevation of corticoid excretion and the low eosinophil counts are compatible either with responsiveness to continuing stress or with compensatory overproduction of adreno-corticotropin following depression of thyrotropin.

It is of interest that the symptoms later identified as those of hypothyroidism first appeared after a prolonged febrile illness, diagnosed as possible infectious mononucleosis. This suggests that an infectious agent may have damaged the adenohypophyseal source of thyrotropin. Current evidence^{12,13} indicates that the basophil cells produce thyrotropin and that a specific spatial group of such cells may be the producers of this hormone.^{14,15} Selective damage to these cells, with sparing of other basophil groups responsible for the production of gonadotropic hormones and perhaps adrenocorticotropin, could explain the presence of an isolated thyrotropin deficiency in our patient.

The appearance of thyrotropin in the serum in October, 1952, after four months' treatment with small doses of L-thyroxin is in contrast to the initial absence of thyrotropin from the serum. This might be explained by the following possibilities: (1) stimulation of secretory activity at the adenohypophyseal source of thyrotropin by thyroxin in small dosage; (2) spontaneous fluctuations in thyrotropin secretion independent of thyroxin effect; or (3) variations in peripheral utilization or excretion of thyrotropin. The first possibility appears most likely. There is evidence that the production or release of thyrotropin is dependent upon the availability of minimal amounts of thyroxin. 16 Also, D'Angelo has encountered responses similar to those in our patient in some cases of panhypopituitarism. 17 The later disappearance of thyrotropin from the serum in May, 1953, is compatible with the inhibitory effect of large doses of L-thyroxin (0.6 mg. daily) upon the output of thyrotropin which might have previously been stimulated by the smaller doses of L-thyroxin. The second possibility appears unlikely in view of the history. The rise in I131 uptake by the thyroid from 3 to 14 per cent at twenty-four hours following

L-thyroxin therapy, concomitant with the appearance of serum thyrotropin, argues against the third possibility and also against the presence of primary hypothyroidism. Assuming that the adenohypophyseal cells responsible for the secretion of thyrotropin were stimulated in this case by small oral doses of L-thyroxin, one would conclude that the primary damage to, or insufficiency of, these cells was incomplete.

The variations in the serum levels of proteinbound iodine prior to treatment may have reflected spontaneous fluctuations in tissue utilization or excretion, or in the rate of hormone release from a hypoactive thyroid. The disparity between the effects of both thyrotropin alone and the growth hormone preparation contaminated with thyrotropin upon the iodineaccumulating capacity of the thyroid and upon serum protein-bound iodine level is of interest. It suggests (1) a difference in the responsiveness of various functions of the thyroid cell to a single tropic stimulus, or (2) a superiority of the I¹³¹ tracer test as a measure of thyroid response to thyrotropin in the differential diagnosis of primary and secondary thyroid deficiencies.

The decrease in intestinal absorption of sugars which occurs in hypothyroidism is perhaps reflected in our patient by the differences between the initial oral and intravenous glucose tolerance curves; the change in oral glucose tolerance to normal after treatment with L-thyroxin (Table II) further favors this thesis.

The possible causes of the slight insulin sensitivity and hypoglycemia unresponsiveness in our patient may now be considered. There was no evidence in support of adrenocortical deficiency or adrenocorticotropic deficiency. Liver function was normal by the standard tests and the blood sugar response to epinephrine indicated normal hepatic glycogen storage and release. The growth hormone preparation produced glycosuria without hyperglycemia (previously reported by others 18); it caused no significant decrease in the insulin sensitivity or in the hypoglycemia unresponsveness. The insulin-glucose tolerance test was performed on the day following the last of four growth hormone injections. On the basis of animal experiments¹⁹ this was considered the optimal technic for demonstration of growth hormone effect on insulin-glucose responses. The potential corrective action of the growth hormone on these abnormalities of insulin-glucose responses should not have been inhibited by the thyrotropin contamination of the preparation

used. (Study Period No. 2, Table II.) Hence, although the possibility was not excluded, intrinsic deficiency of growth hormone or related insulin antagonizing factor could not be demonstrated to be the cause of the patient's insulin sensitivity and hypoglycemia unresponsiveness. The patient's ability to tolerate a twenty-four-hour fast without development of hypoglycemia further argues against growth hormone deficiency. Hypothyroidism does not cause insulin sensitivity or hypoglycemia unresponsiveness except as a reflection of secondary adrenocortical depression.⁵ In our patient adrenocortical function was normal and eleven months' treatment with L-thyroxin in ascending doses up to 0.6 mg. daily failed, as did also exogenous thyrotropin, to alter significantly the insulin sensitivity or hypoglycemia unresponsiveness. By exclusion, therefore, mild functional hyperinsulinism remains as the most likely cause of the slight but definite abnormalities in insulin sensitivity and hypoglycemia responsiveness. The symptoms (faintness, sweating and nervousness after fasting, relieved by food) originally suggestive of hypoglycemia were entirely relieved by large doses of L-thyroxin.

The cause of the acetone-like odor on the breath was not determined. This phenomenon disappeared when L-thyroxin was administered in large doses.

SUMMARY

An unusual case of hypothyroidism in a twenty-seven year old white male is reported. The existence of solitary or 'monotropic' thyrotropin deficiency was suggested by the responses to exogenous thyrotropin and other studies, and by the evidence indicating integrity of other adenohypophyseal hormones.

Slight insulin sensitivity and hypoglycemia unresponsiveness were present. Study of these abnormalities included the testing of responses to administration of a growth hormone preparation. We could attribute these abnormalities neither to anterior pituitary nor adrenocortical

deficiency.

The patient's symptoms responded both to intramuscular thyrotropin and oral sodium L-thyroxin.* The implications of this case are discussed with special reference to the cytologic

*Thyrotropin and growth hormone preparations were kindly supplied by Armour and Company, Chicago, Illinois and sodium L-thyroxin as elthrin® by Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

source of thyrotropin and the influence of L-thyroxin therapy on serum thyrotropin activity.

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Orthostatic Hypotension and Orthostatic Tachycardia*

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RTHOSTATIC hypotension is an interesting condition in which the reflex mechanisms normally operating to maintain blood pressure against the effect of gravity are absent or greatly diminished. A profound fall in blood pressure occurs in the standing position, the systolic pressure may fall to 40 mm. Hg and the diastolic to 0. The critical level of blood pressure below which reported patients with orthostatic hypotension developed symptoms was a systolic of approximately 50 mm. Hg. Normal persons are frequently symptomatic with a drop in systolic pressure from 110 to 90 mm. Hg, and more severe symptoms may develop if the systolic pressure falls to lower levels.

In 1925 Bradbury and Eggleston¹ reported three cases in which syncopal attacks occurred after standing erect for some minutes or during physical exertion. In addition to orthostatic hypotension other features presented by these patients were a slow unchanging pulse, inability to perspire, nocturia, lowered basal metabolism and indefinite changes in the nervous system. These authors concluded that the symptoms were due to paralysis of the sympathetic vasoconstrictor endings.

In 1952 Rosecan et al.² collected thirty-seven cases of orthostatic hypotension from the literature. In their study they included only those patients with postural hypotension, anhidrosis and impotence (the latter first described by East and Brigden³). They differentiated two types of orthostatic hypotension: (1) Those cases in which the hypotension was present as a manifestation of a definite disease entity, namely, tabes dorsalis, diabetes mellitus, Addison's disease, hypopituitarism, syringomyelia and hematomyelia, multiple sclerosis, subacute combined degeneration and postsympathectomy. (2) Those cases due to unknown or ill defined disease of the central nervous system.

The following case report represents an example of the second type. This patient demonstrates most of the characteristic findings of the idiopathic variety and in addition has orthostatic tachycardia.

CASE REPORT

A forty year old white, married, male railroad worker entered the Denver V. A. Hospital for the second time on December 22, 1953. His chief complaint was of recurrent blackout spells of ten years' duration. The spells occurred with varying frequency and had become worse in the preceding three years. The episodes were more frequent and more severe during the summer months. The attacks were characterized by blurring of vision, spots before the eyes, dizziness, weakness and a sensation of wind blowing in his ears. They were precipitated by changes in position and physical exertion such as climbing stairs. Arising from bed in the morning invariably resulted in an attack relieved only by lying down. These episodes would last a few minutes and disappear spontaneously or would persist until the patient assumed a supine position. They were sometimes accompanied by intense occipital headache and nausea with repeated vomiting. These spells had never been associated with an aura, involuntary movements, loss of consciousness or incontinence.

In the preceding year and a half the patient had noticed loss of libido with difficulty in maintaining an erection and failure to achieve ejaculation, despite the occurrence of orgasm. During the preceding ten years there had been absence of sweating. Nocturia two to three times has been present for several years.

His admission to the hospital was recommended by his family physician for low blood pressure and possible Addison's disease. The discharge diagnosis on his first admission in August, 1953, was conversion reaction mani-

^{*} From the Medical Service, Denver Veterans Administration Hospital, Denver, Colo.

fested by emotional instability and transient blindness.

Past history revealed that the patient had been married seventeen years and had a fourteen year old daughter in good health. His mother died of cancer at the age of forty-five. limits, no murmurs were heard. The abdomen was scaphoid in appearance; liver, kidney, spleen were not palpable and no abnormal masses or tenderness were present. The genitalia were normal. Rectal examination was negative. Traumatic amputation of the right little finger

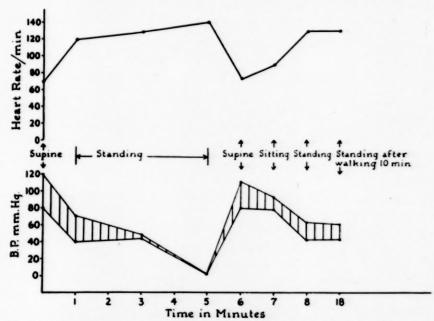


Fig. 1. The effect of change in position on blood pressure and heart rate in a patient with orthostatic hypotension and tachycardia.

The patient had uncomplicated measles and mumps in childhood. At the age of twenty-four he had fallen from a bicycle and was told by his family that his talk did not make sense for two weeks; he was not seen by a doctor at this time and did not remember any of the details of this injury. In 1943 he was hospitalized in the army for an episode of dizziness, headache and vomiting. X-rays of the gastrointestinal tract showed no abnormality.

The patient was a well developed, well nourished, white man who appeared younger than his stated age of forty. The blood pressure was 90/60 in both arms with patient sitting, pulse 96 and regular, temperature 98.6°F., weight 150 pounds. The pupils were equal and symmetric and reacted to light and accomodation. External ocular movements were normal. Funduscopic examination was negative. The nose, ears, mouth, throat and teeth showed no abnormalities. The lungs were clear to auscultation and percussion. Examination of the heart showed A2 greater than P2, sinus rhythm was present, the left heart border was within normal

was noted. No abnormalities were detected in the neurologic examination.

Hemogram showed hemoglobin 14.5 gm., hematocrit 40 per cent, white blood count 6,500 with a normal differential. Serologic tests were negative. The urine was normal. The fasting blood sugar was 72 mg. per cent, urea nitrogen 16 mg. per cent, sodium 148 mEq., potassium 4.9 mEq., chloride 105 mEq., carbon dioxide 24 mEq. Spinal fluid examination showed an initial pressure of 90 mm. H₂O, two cells, 19 mg. per cent protein, serological tests negative. Urinary 17-ketosteroids, 12.8 mg./twenty-four hours. Chest x-ray and skull films were negative. Electrocardiogram and electroencephalogram were normal.

HEMODYNAMIC STUDIES

Figure 1 shows the changes in blood pressure and pulse resulting from changes in position. The pressure fall to 50/40 upon assuming the erect position resulted in subjective complaints of tightness in the head, dimness of vision, weak-

ness and dizziness. These symptoms disappeared with restoration of blood pressure and pulse after the patient resumed the horizontal position. Transient symptoms resulted when the pressure dropped to 62/42 after the patient rose from sitting. The critical level of blood pressure at

minutes with the patient supine. In the erect position the pressure dropped to 76/58 in one minute and in ten minutes was 110/66. Symptoms did not appear since the critical level of blood pressure was not reached. Discontinuance of L-nor-epinephrine with the patient erect

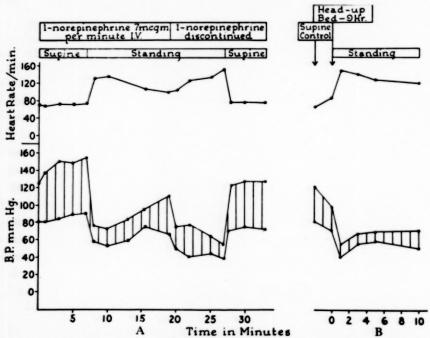


Fig. 2. A, the effect of L-norepinephrine on orthostatic hypotension and tachycardia. B, head of bed elevated 1.5 feet for nine hours; effect of change in position on blood pressure and pulse.

which symptoms developed in this patient was 50 to 60 mm. Hg systolic.

Application of elastic bandages to the legs and blood pressure cuffs to the thighs inflated to 90 mm. Hg failed to prevent the precipitous fall in blood pressure and the tachycardia. A snug abdominal binder and the administration of 25 mg. of ephedrine likewise had no effect, although the latter raised the systolic pressure 15 mm. Hg with the patient supine. When the blood pressure cuffs about the thighs were inflated to 250 mm. Hg a slight rise in pressure resulted with the patient supine. In the erect position the pressure dropped to 78/50. Symptoms did not develop since critical levels were not exceeded. Removal of the cuffs with the patient erect resulted in further fall in blood pressure, tachycardia and symptoms.

Figure 2 shows the effect of 8 mg. of L-nor-epinephrine (levophed®) in 1,000 cc. of 5 per cent dextrose in water, given intravenously at a constant rate of 7 μ g. per minute. This increased the blood pressure to 154/90 in seven

resulted in progressive blood pressure fall, tachycardia and symptoms. Normal pressure and pulse returned within one minute after the supine position was assumed.

Also illustrated in Figure 2 is the effect of the head-up bed on blood pressure and pulse. Nine hours after sleeping in the head-up bed the patient's blood pressure was 98/70, significantly lower than his normal supine pressure. Within one minute after arising his pressure was 54/40 and heart rate 148. Transient symptoms developed. After ten minutes in the erect position his pressure rose to 70/50, the tachycardia decreased and no symptoms were present

The complaint of nocturia occurring in this patient was evaluated by comparing the urinary volume and excretion of sodium, chloride and potassium with the patient erect and supine. Figure 3 shows significant decrease in urinary volume and urinary sodium, chloride and potassium excretion with the patient erect.

Renal clearance studies were carried out in this patient employing a standard continuous

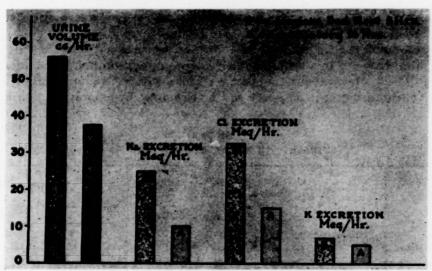


Fig. 3. Comparison of the urine volume, Na, Cl and K excretion in the supine and erect positions.

infusion technic. With the patient on a tilt table the glomerular filtration rate (as determined by inulin clearance) and renal plasma flow (as determined by PAH clearance) were measured in the horizontal and erect position. Control studies were made with the patient horizontal for three consecutive fifteen-minute periods. He was then tilted to the erect position over a period of six minutes. Studies were again carried out over four consecutive fifteen-minute periods with the patient tilted back to the horizontal position. Simultaneous with the above the rate of urinary excretion of sodium, chloride and potassium was determined.

Table I summarizes the renal clearance data. Accompanying orthostatic hypotension in this patient were decreased renal plasma flow and glomerular filtration rate. Shortly after replacing the patient to the horizontal position normal values were re-established. Similar decreases in sodium, chloride and potassium excretion occurred. However, with return to the supine position the excretory rates of sodium and chloride remained well below control values while potassium excretion exceeded control values.

COMMENTS

Ellis and Haynes⁴ first demonstrated that patients with orthostatic hypotension did not pool more blood in the lower part of the body than do normal subjects under similar circumstances. What occurs is that pooling of a normal amount of blood results in an abnormal blood pressure fall. Stead and Ebert⁵ confirmed this

and concluded that the reflex vasoconstriction which maintains the arterial pressure in normal subjects is absent in patients with orthostatic hypotension. This loss of reflex vasoconstriction in response to fall in arterial pressure is the fundamental disturbance in postural hypotension.

MacLean et al.^{6,7} hold that orthostatic hypotension and orthostatic tachycardia are disorders of venous return. They propose that the circulatory defect caused by inadequate venous return in the erect position is either a direct result of pooling of abnormal quantities of blood in the lower extremities or a result of very rapid transudation of circulating fluid into the tissues of the lower extremities. The rapidity of onset of the deficiency when the upright position is assumed and the instantaneous recovery in the recumbent state suggested to these authors that the defect is the result of pooling of blood in the capillary venous bed.

Hickam and Pryors correlated cardiac output with blood pressure fall in twelve patients with orthostatic hypotension. They concluded that postural hypotension resulted primarily from inadequate arteriolar constriction with the patient erect. The degree of hypotension was often intensified by a large fall in cardiac output although this did not occur consistently. The decreased cardiac output was ascribed to diminished return of venous blood to the heart as the result of abnormal dilation of the venous system with the patient erect.

In two cases of orthostatic hypotension recently studied by Luft and von Euler⁹ a marked decrease in the spontaneous urinary 884

excretion of nor-epinephrine and epinephrine was found to occur.

Orthostatic hypotension is classified by Stead and Ebert⁵ as a disease of the sympathetic nervous system. Their observations indicate that the loss of vasoconstriction in response to patients. After returning the patients to a recumbent position they observed that sodium excretion was not restored immediately in spite of prompt restoration of the filtered sodium load. This decreased sodium excretion in patients with orthostatic hypotension, when in the erect posi-

TABLE I SUMMARY OF RENAL CLEARANCE DATA

Time (min.)		Blood Pressure (mm. Hg)	Clearance 1.73 sq. m.			Electrolyte Excretion					
	Position		Inulin (cc./min.) PAH (cc./min.	DALI	Filtration Fraction (%)	Na		Cl		К	
				(cc./min.)		P†	UV†	P†	UV†	P*	UV
	Supine:										
0-15	Control	120/75	99.2	509.0	19.5	140	217	104	200	4.15	89
15-30	Control	120/80	103.2	515.1	20.0	139	249	104	224	4.15	95
30-45	Control	130/80	108.2	562.3	19.2	139	278	103	242	4.03	97
	Mean		103.5	528.7	19.6		248		222		90
	Tilt degree:										
	0	126/76									
	22	100/70									
	30	88/64									
45-51	40	60/50	61.7	336.5	18.3		168		150		57
	45	75/50									
	60	50/40									
	90	0/0									
	Supine:										
51-66	Control	120/74	92.4	476.7	19.4	137	96	104	100	4.03	108
66-81	Control	114/74	97.7	507.1	19.3	141	119	105	133	3.80	129
31-96	Control	110/70	94.9	528.6	17.9	140	151	105	138	3.88	98.7
96-111	Control	124/72	100.6	534.9	18.8	143	171	105	135	3.53	61.0

^{*} µEq./cc. (uncorrected for Donnan).

 $t \mu Eq./min./1.73 sq. m.$

blood pressure fall is produced by lesions in sympathetic centers or their efferent fibers in the central nervous system rather than in peripheral portions of the reflex arc. Depending on the extent and localization of the lesions the patient may display only loss of reflex vasoconstriction or, in addition, other manifestations of impaired sympathetic function such as anhidrosis, impotence and absence of increased heart rate in response to lowered blood pressure.

In 1942 Corcoran et al.¹⁰ first described decreased glomerular filtration and renal plasma flow in patients with orthostatic hypotension. Bachman and Youmans¹¹ observed large decreases in the rate of sodium and chloride excretion and glomerular filtration (as determined by endogenous creatinine clearance) in these

tion, is considered to be due in part to a decrease in sodium filtered at the glomerulus and in part to changes in tubular reabsorption that are independent of the filtered sodium load. Changes in the excretion of chloride parallel those of sodium.

The renal clearance data obtained in this patient with orthostatic hypotension confirm those of Bachman and Youmans. 11 The relation of the filtered sodium and chloride load to the rate of urinary excretion of sodium and chloride is shown in Figure 4. The prompt restoration of the filtered sodium and chloride load occurring after the patient was replaced to a horizontal position was not accompanied by restoration of the sodium and chloride excretory rates. This discrepancy suggests that increased tubular reabsorption of these ions took place.

TREATMENT

The treatment of orthostatic hypotension may be divided into three phases: (1) That of the underlying disease of which orthostatic hypotension is merely a manifestation. (2) Mechanical measures such as abdominal binders and 2. Various measures including elastic bandages to the legs, abdominal binder and administration of ephedrine were unsuccessful in preventing postural hypotension and tachycardia and the accompanying symptoms in this patient. The head-up bed, continuous intra-

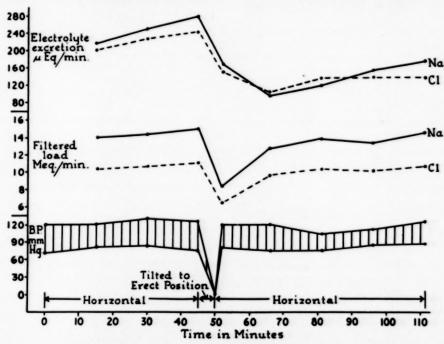


Fig. 4. Comparison of filtered Na and Cl loads with Na and Cl excretion in orthostatic hypotension.

elastic stockings which are designed to prevent pooling of blood in the lower part of the body. MacLean and Allen⁶ introduced the head-up bed as a therapeutic measure. They contend that this position prevents the loss of that measure of postural adaptation which the patient himself has gained while in an erect position. (3). Various sympathomimetic agents such as ephedrine, paredrine® and epinephrine in oil have been used with limited success for orthostatic hypotension. Gregory¹² and others have described the use of salt and desoxycorticosterone to increase the blood volume and hence the blood pressure in these patients. None of these measures will effect cure but their judicious use, together with a sufficient explanation of the basic disease to the patient, may go far in restoring him to normal activity.

SUMMARY

1. The case report of a patient with orthostatic hypotension and tachycardia, anhidrosis, impotence and nocturia is presented.

venous infusion of L-nor-epinephrine and blood pressure cuffs inflated to 250 mm. Hg to both thighs did not prevent orthostatic hypotension and tachycardia. However, a drop in pressure below critical levels did not occur, hence symptoms did not result.

Renal clearance studies employing a standard continuous infusion technic showed decreased glomerular filtration and renal plasma flow, with decreased excretion of sodium, chloride and potassium accompanying orthostatic hypotension.

- 3. Orthostatic hypotension is a disease of the sympathetic nervous system, probably of the sympathetic centers in the hypothalamus or efferent tracts in the central nervous system, or both.
- 4. Treatment is discussed. It includes such measures as abdominal binders, elastic stockings, the head-up bed and administration of sympathomimetic drugs and desoxycorticosterone and salt.

Acknowledgment: The author wishes to express his appreciation to Dr. Neal S. Bricker and

Charles J. Hlad, Jr., M.S., for performing the renal clearance studies in this case.

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Hepatocellular Adenomatosis*

Report of a Case with Liver Function Studies

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and because it is apparently the first to be reported in which a patient with this unusual liver lesion was adequately studied clinically. In most similar cases in the literature the liver is described as cirrhotic or otherwise scarred. ¹⁻¹⁵ The latter changes make it problematic whether one is dealing with true adenomas, with focal areas of cirrhosis or with the more common regenerating nodules so often associated with portal and other diffuse cirrhoses. ^{2,3,5,15} The absence of fibrosis or scarring in the present case is stressed.

CASE REPORT

P. M., a twenty-seven year old Negro male, developed scrotal and ankle edema while in the military service early in 1951. Hospitalization revealed hypoproteinemia, anasarca, marked proteinuria with a normal blood pressure, and slight elevation of serum globulin and cholesterol levels. He was thought to have glomerulo-nephritis (nephrotic syndrome) which progressed with gradually increasing oliguria until he died on March 4, 1953. His past history and family history were non-contributory.

Following a paracentesis in May 1951, he developed what appeared to be acute peritonitis. From this time until death he had many attacks of severe, crampy, abdominal pain which finally became localized in the epigastrium late in 1952. Occasional paracenteses produced a milky fluid. During the last three months of life he had several loose, blood-tinged stools daily. A few of these contained a moderate amount of fat and were somewhat bulky. Several times during 1952 and just prior to death he had tonic seizures involving all extremities and lasting one to two minutes.

Serum calcium and inorganic phosphorus

levels ranged from 7.5 to 8.0 and 3.9 to 4.9 mg. per cent, respectively. Blood urea nitrogen rose gradually to 72 mg. per cent during the last few weeks of life. Total serum cholesterol fell from 320 mg. per cent early in the illness to 190 mg. per cent later on. Total serum proteins finally fell to as low as 3.5 gm. per cent, with 1.0 gm. per cent albumin.

Repeated liver function studies during the last eighteen months of life revealed 3 and 4 plus cephalin flocculation tests, serum alkaline phosphatase 40–48 Shinowara units (normal 2.2–8.6 units) thymol turbidity 10–12 units, and bromsulfalein retention 32 per cent in forty-five minutes. The serum bilirubin was always well within normal limits and the patient was never clinically jaundiced. His prothrombin time was usually 24 to 28 seconds, controls 14 to 17 seconds, and he was hypersensitive to dicumarol, his prothrombin time rising to seventy-two seconds following a single 200 mg. dose.

The congo red dye retention, blood sickling preparations and blood VDRL were all negative. Fasting blood sugar was within normal limits. Chest x-rays, gastrointestinal series, barium enemas and intravenous pyelograms were negative. The hemogram was unremarkable except for a mild hypochromic anemia and occasional leukocytosis associated with the abdominal pain.

Autopsy was performed six hours postmortem. The body was emaciated, poorly developed, weighed an estimated 90 pounds and measured 5 feet 4 inches in length. The liver was reduced in size (weight 750 gm.), deformed in shape and had a slightly thickened, pale gray capsule. There was a deep depression on the superior diaphragmatic surface partly separating the right and left lobes in the region of the falciform ligament. (Fig. 1.) The outer surfaces every-

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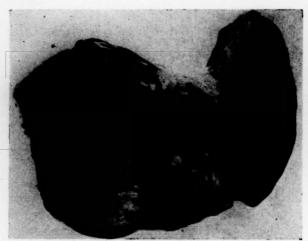


Fig. 1. Multiple adenomas throughout liver and mild fibrous capsular thickening.

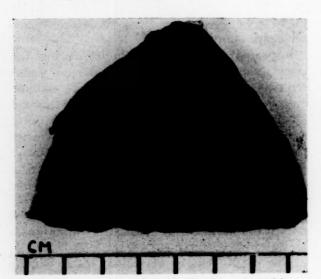


Fig. 2. Cut surface of formalin-fixed portion of liver illustrating various sized adenomas within many of which there are irregular, dark, blood-filled spaces. Note compression of blood vessels by large adenomas on right and uniform lobular pattern of non-nodular liver.

where, as well as the cut surfaces, were studded with countless bulging, rubbery, red-brown tumor nodules which were slightly firmer than the intervening parenchyma. The tumor nodules, however, were not separated by fibrous bands such as are characteristic of cirrhotic livers. The adenomas ranged from 0.2 to 1.5 cm. in diameter and most of them were roughly spherical but occasional nodules appeared to consist of several smaller ones. (Fig. 2.) The liver cut without increased resistance. A few of the larger growths just beneath the liver capsule had umbilicated centers. Lobular patterns were not evident within the tumor masses. In places intrahepatic veins appeared to be compressed by adjacent nodules.

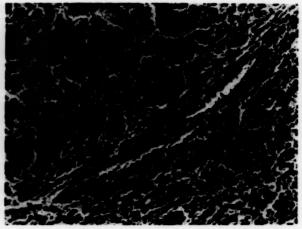


Fig. 3. A portion of large adenoma illustrating irregular, radiating adenoma cell cords, upper left, and atrophic surrounding liver cells, lower right; hematoxylin and eosin stain, × 144.

Nowhere in the liver was there any evidence of scarring. Although quite well demarcated from the intervening, somewhat compressed but normally lobulated, chocolate-brown parenchyma, none of the adenomas appeared encapsulated. There was mild to moderate sclerosis of the portal vein and its major tributaries, particularly the splenic vein.

The spleen was firmer, more fibrous than usual, and weighed 130 gm. There was almost complete replacement of the pancreas by dense, firm fibrous tissue, fat and flecks of fat necrosis. The pancreatic ducts were unremarkable. Each kidney weighed 100 gm. and their dark red surfaces were studded with numerous small clusters of pale yellow, granular excrescences. The usual cortical striations were replaced by pale yellow streaks and the cortices were reduced in thickness, averaging 0.3 to 0.4 cm. in width. The pelves, calyces and ureters were unremarkable. The heart was small (weight 165 gm.) and the myocardium dark brown. The lungs together weighed 330 gm. and also seemed reduced in size.

Microscopically, the liver nodules were not as sharply demarcated from the surrounding parenchyma as they appeared to be on gross examination. (Fig. 3.) Nowhere in or about the growths or in the intervening parenchyma was there any suggestion of cirrhosis, scarring, inflammatory reaction or invasion of blood vessels. Most of the adenomas were composed chiefly of more or less radially arranged, closely packed, anastomosing strands of hepatic cord type cells. Occasional ones consisted partly of

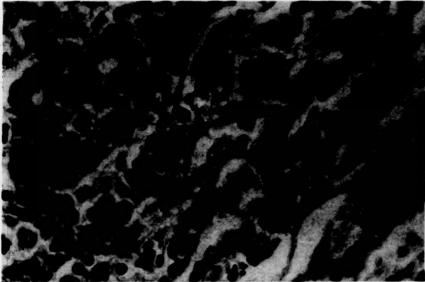


Fig. 4. High power magnification of edge of adenoma illustrating tubule formation and difference in size between adenoma cells on upper left and atrophic cells, lower right; hematoxylin and eosin stain, \times 475.

irregular, blood-filled endothelium-lined spaces, and near the periphery of many of the nodules the sinusoids were markedly congested. In many adenomas some of the hepatic cord type cells formed single-layered tubular structures which occasionally contained a bile plug. (Fig. 4.) One or more normal or compressed portal areas were variously situated in occasional new growths. Most of the tumor cells, although normal in size, were appreciably larger than those of the intervening parenchyma. The cytoplasm of the larger cells was usually more intensely eosinophilic and also contained much less basophilic material (thought to represent nucleic acids16) and glycogen than the smaller intervening cells.

There was moderate thickening of the splenic sinus walls. The sinuses were widened and their lining cells were more prominent than usual. Sections of pancreas revealed widespread old and recent fat necrosis in addition to extensive scarring and replacement by fat. In the kidneys the basement membranes of the glomerular tufts were almost universally thickened and hyalinized. A few tufts were completely hyalinized and most were lobulated. Abundant fat was noted in the epithelium and lumina of the proximal and distal convoluted tubules. The blood vessels were everywhere unremarkable. Sections stained for the presence of amyloid were negative.

The principal anatomic diagnoses were chronic glomerulonephritis, acute and chronic

pancreatitis with fat necrosis, brown atrophy of the liver and heart, chronic passive congestion of the spleen and hepatocellular adenomatosis.

COMMENTS

Both in their gross and histologic characteristics the adenomas resembled those described in the literature. ¹⁻¹⁵ However, a fairly extensive review of the subject failed to reveal a single case in which the tumors were so numerous, in such a small liver, and associated with abnormal liver function tests. ^{1-15,17} The vast majority of the reported cases, it is true, antedated liver function tests. Ranström¹⁷ recently reported a case of multiple liver cell type adenomas in an enlarged liver but, since there was a history of gold therapy, it may be that in his case the nodules represented hyperplasia.

The complete absence of cirrhosis, scarring, inflammation or jaundice in the present case deserves emphasis. The patient was not known to have been exposed to any hepatotoxins.

The small size of the liver despite the presence of the numerous tumors merits comment. In cases of primary malignant tumors of the liver the latter often is not enlarged and is sometimes reduced in size. It may be that the prolonged severe starvation and hypoproteinemia due to the pancreatic and renal diseases played an important role in the generalized visceral atrophy including the liver, spleen, pancreas, heart and skeletal muscle. Some degree of compression atrophy of the intervening paren-

chyma may have been caused by the multiple expanding growths. Although the spleen was not enlarged by ordinary standards, it was relatively increased in size as compared with the liver and heart, and histologically there was ample evidence of chronic passive congestion. In view of the changes in the spleen, the portal vein sclerosis and the clinical evidence of liver dysfunction, it is suggested that portal hypertension may have contributed to the ascites in this case. It may be that the portal hypertension was due to compression of intrahepatic veins by expanding adenomas acting like the regenerated nodules in portal cirrhosis as postulated by Kelty, Baggenstoss and Butt. 19

SUMMARY

A case of hepatocellular adenomatosis in a non-cirrhotic liver is presented. It is believed to be the first case of this type described in which liver function studies were made during life.

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Erratum: The article entitled "Some Variations in the Clinical Picture of Congenital Defect of the Interventricular Septum" by Dr. Noble O. Fowler, which appeared in the September 1954 issue of The American Journal of Medicine omitted to make mention of the fact that the work had been done at the Cardiac Laboratory of the Brooklyn Hospital, and the Department of Medicine of the State University of New York at New York City.

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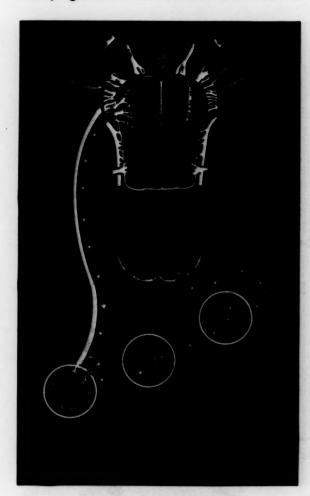
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^{1.} Schwartz I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: Gastroenterology 25:416 (Nov.) 1953.

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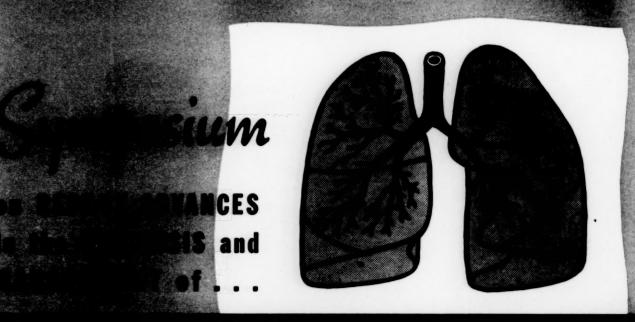




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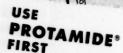


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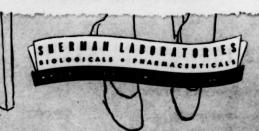


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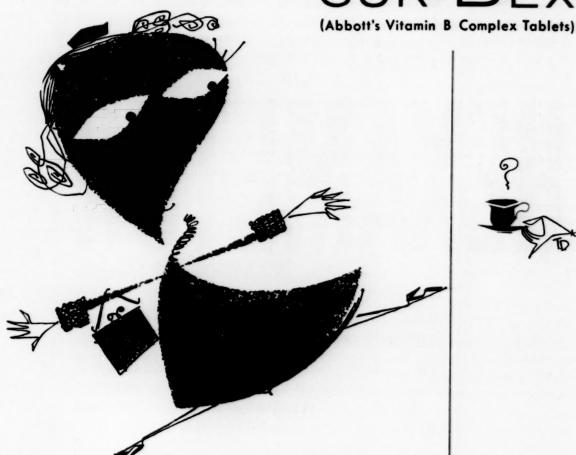
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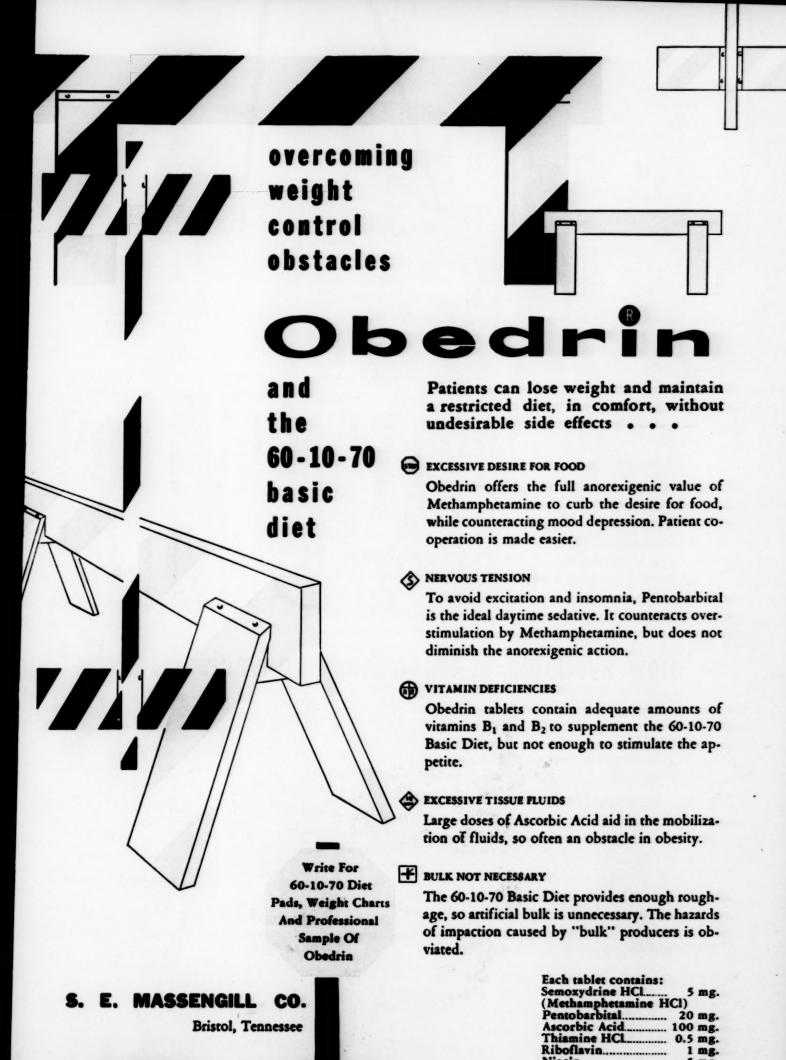
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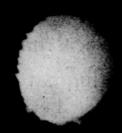
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1. Parish, F. A.: M. Times; in press. 2. Menger, H. C.: New York State J. Med.; in press.

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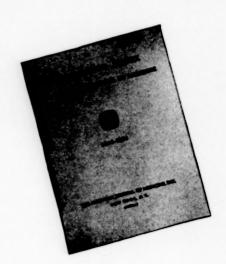
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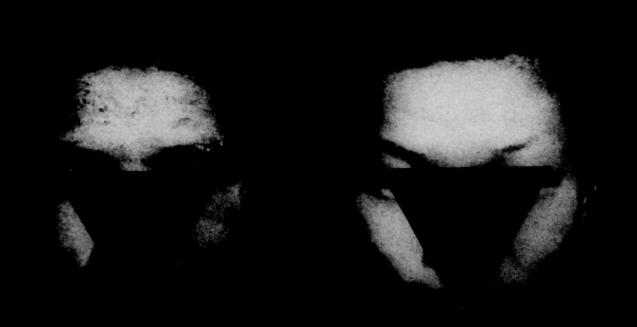
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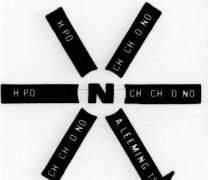
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1. Gross, F., and Tschopp, E.: Experientia 8:75, 1952. 2. Thorn, G. W., and Jenkins, D.: In press. 3. Thorn, G. W.; Jenkins, D.; Arons, W. L., and Frawley, T. F.: Schweiz. med. Wchnschr. 82:697, 1952. 4. Gaunt, R.; Leathem, J.; Howell, C., and Antonchak, N.: Endocrinology 50:521, 1952. 5. Sorkin, S. Z., and Soffer, L. J.: Am. Fed. Clin. Research, May 4, 1952.

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*Aaron, H.: Weight Control, Consumer Reports 17:100 (Feb.) 1852.



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- Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared, United States Department of Agriculture, Agricultural Handbook no. 8, 1950.
- Data furnished by the Laboratories of The American Institute of Baking, Chicago, Illinois.
- Sebrell, W.H., Jr.: Trends and Needs in Nutrition, J.A.M.A. 152:42 (May 2) 1953.
- Flour and Bread Enrichment, 1949-50, The Committee on Cereals, Food and Nutrition Board, National Research Council, 1950.



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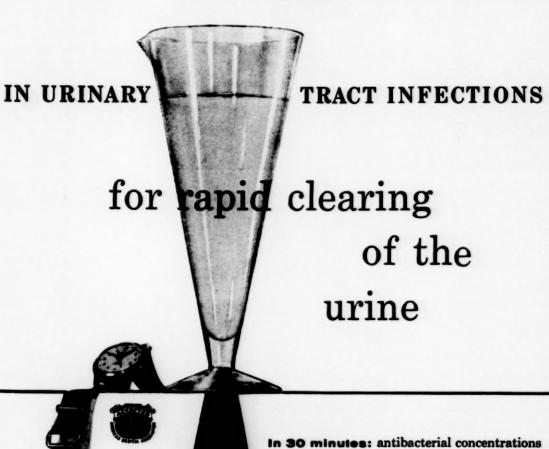
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